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Rheology

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INTRODUCTION

The term rheology, from the Greek *rheo* (to flow) and *logos* (science), was suggested by Bingham and Crawford (as reported by Fischer¹) to describe the flow of liquids and the deformation of solids. Viscosity is an expression of the resistance of a fluid to flow; the higher the viscosity, the greater the resistance. As will be seen later, simple liquids can be described in terms of absolute viscosity. The rheologic properties of heterogeneous dispersions are more complex, however, and cannot be expressed by a single value.

In recent years, the fundamental principles of rheology have been used in the study of paints, inks, doughs, road building materials, cosmetics, dairy products, and other materials. The study of the viscosity of true liquids, solutions, and dilute and concentrated colloidal systems is of much practical as well as theoretic value. These points have been discussed in Chapter 15, which deals with colloids. Scott-Blair² recognized the importance of rheology in pharmacy and suggested its application in the formulation and analysis of such pharmaceutical products as emulsions, pastes, suppositories, and tablet coatings. The manufacturer of medicinal and cosmetic creams, pastes, and lotions must be capable of producing a product with an acceptable consistency and smoothness and must be able to reproduce these qualities each time a new batch is prepared. In many industries, the judgment of proper consistency is made by a trained person with long experience who handles the material periodically during manufacture to determine its "feel" and "body." The variability of subjective tests at different times under varying environmental conditions is, however, well recognized. A more serious objection, from a scientific standpoint, is the failure of subjective methods to distinguish the various properties that make up the total consistency of the product. If these individual

physical characteristics are delineated and studied objectively according to the analytic methods of rheology, valuable information can be obtained for use in formulating better pharmaceutical products.

Rheology is involved in the mixing and flow of materials, their packaging into containers, and their removal prior to use, whether this is achieved by pouring from a bottle, extrusion from a tube, or passage through a syringe needle. The rheology of a particular product, which can range in consistency from fluid to semisolid to solid, can affect its patient acceptability, physical stability, and even biologic availability. Thus, viscosity has been shown to affect the absorption rate of drugs from the gastrointestinal tract.

The rheologic properties of a pharmaceutical system can influence the choice of processing equipment to be used in its manufacture. Furthermore, lack of appreciation for the correct choice of a piece of processing equipment can result in an undesirable product, at least in terms of its flow characteristics. These and other aspects of rheology that apply to pharmacy are discussed by Martin et al.³

When classifying materials according to the types of flow and deformation, it is customary to place them in one of two categories: Newtonian or non-Newtonian systems. The choice depends on whether or not their flow properties are in accord with Newton's law of flow.

NEWTONIAN SYSTEMS

Newtonian's Law of Flow. Consider a "block" of liquid consisting of parallel plates of molecules, similar to a deck of cards, as shown in Figure 17-1. The bottom layer is considered to be fixed in place. If the top plane of liquid is moved at a constant velocity, each lower layer will move with a velocity directly proportional to

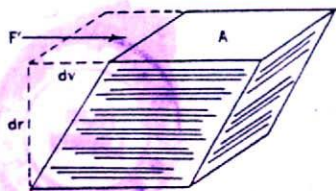


Fig. 17-1. Representation of the shearing force required to produce a definite velocity gradient between the parallel planes of a block of material.

its distance from the stationary bottom layer. The difference of velocity dv between two planes of liquid separated by an infinitesimal distance dr is the *velocity gradient* or *rate of shear*, dv/dr . The force per unit area F'/A required to bring about flow is called the *shearing stress* and is given the symbol F' . Newton was the first to study the flow properties of liquids in a quantitative way. He recognized that the higher the viscosity of a liquid, the greater the force per unit area (*shearing stress*) required to produce a certain rate of shear. Rate of shear is given the symbol G . Hence, the rate of shear should be directly proportional to the shearing stress, or

$$\frac{F'}{A} = \eta \frac{dv}{dr} \quad (17-1)$$

in which η is the *coefficient of viscosity*, usually referred to simply as *viscosity*.

Equation (17-1) is frequently written as

$$\eta = \frac{F}{G} \quad (17-2)$$

in which $F = F'/A$ and $G = dv/dr$. A representative flow curve, or *rheogram*, obtained by plotting F versus G for a Newtonian system is shown in Figure 17-2a. As implied by equation (17-2), a straight line passing through the origin is obtained.

The unit of viscosity is the *poise*, defined with reference to Figure 17-1 as the shearing force required to produce a velocity of 1 cm/sec between two parallel planes of liquid each 1 cm² in area and separated by a distance of 1 cm. The cgs units for the poise are dyne sec cm⁻² (that is, dyne sec/cm²) or g cm⁻¹ sec⁻¹ (that is, g/(cm sec)). These units are readily obtained by a dimensional analysis of the viscosity coefficient. Rearranging equation (17-1) to

$$\eta = \frac{F' \, dr}{A \, dv} = \frac{\text{dynes} \times \text{cm}}{\text{cm}^2 \times \text{cm}/\text{sec}} = \frac{\text{dyne sec}}{\text{cm}^2}$$

gives the result

$$\frac{\text{dyne sec}}{\text{cm}^2} = \frac{\text{g} \times \text{cm}/\text{sec}^2 \times \text{sec}}{\text{cm}^2} = \frac{\text{g}}{\text{cm sec}}$$

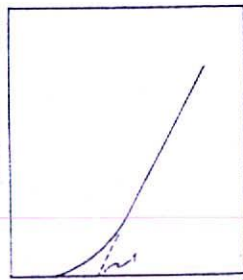
A more convenient unit for most work is the *centipoise* *cp* (plural, *cps*), 1 cp being equal to 0.01 poise. *Fluidity*, ϕ , a term sometimes used, is defined as the reciprocal of viscosity:

Newtonian Law:

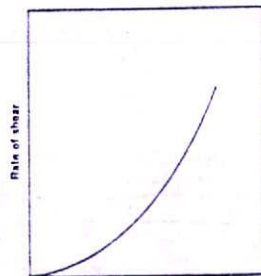
Rate of the shear
is directly
Proportional to the
Shearing stress



Shearing stress
(a) Newtonian flow



Shearing stress
(b) Simple plastic flow



Shearing stress
(c) Simple pseudoplastic flow



Shearing stress
(d) Dilatant flow

Fig. 17-2. Representative flow curves for various materials.

$$\phi = \frac{1}{\eta} \quad (17-3)$$

Kinematic Viscosity. The U.S. Pharmacopeia includes an explanation of *kinematic viscosity*, which is the absolute viscosity as defined in equation (17-1) divided by the density of the liquid at a definite temperature:

$$\text{kinematic viscosity} = \frac{\eta}{\rho} \quad (17-4)$$

The units of kinematic viscosity are the *stoke* (s) and the *centistoke* (cs). Arbitrary scales, Saybolt, Redwood, Engier, and others, for the measurement of viscosity are used in various industries; these are sometimes converted by use of tables or formulas to absolute viscosities and vice versa.

Example 17-1. (a). Using an Ostwald viscometer (see Fig. 17-11), acetone was measured and found to have a viscosity of 0.313 cp at 25° C. Its density at 25° C is 0.788 g/cm³. What is the kinematic viscosity of acetone at 25° C?

(b) Water is ordinarily used as a standard for viscosity of liquids. Its viscosity at 25° C is 0.8904 cp. What is the viscosity of acetone relative to that of water (relative viscosity, η_{rel}) at 25° C?

(a) kinematic viscosity = 0.313 centipoise \div 0.788 g/cm³ = 0.397 poise/(g/cm³) or 0.397 centistokes.

(b) $\eta_{rel(\text{acetone})} = 0.313 \text{ cp} / 0.8904 \text{ cp} = 0.352$ (dimensionless).

The viscosity of some liquids commonly used in pharmacy are given in Table 17-1 at 20° C. A number of viscosity-increasing agents are given in the U.S. Pharmacopeia XXII, p. 1858.

Temperature Dependence and the Theory of Viscosity. While the viscosity of a gas increases with temperature, that of a liquid decreases as the temperature is raised, and the fluidity of a liquid, the reciprocal of viscosity, increases with temperature. The dependence of the viscosity of a liquid on temperature is expressed approximately for many substances by an equation analogous to the Arrhenius equation (p. 295) of chemical kinetics:

$$\eta = A e^{E_a/RT} \quad (17-5)$$

in which A is a constant depending on the molecular weight and molar volume of the liquid, and E_a is an "activation energy" required to initiate flow between the molecules.

The energy of vaporization of a liquid is the energy required to remove a molecule from the liquid, leaving a "hole" behind equal in size to that of the molecule that

has departed. A hole must also be made available in a liquid if one molecule is to flow past another. The activation energy for flow has been found to be about one third that of the energy of vaporization, and it can be concluded that the free space needed for flow is about one third the volume of a molecule. This is presumably because a molecule in flow can back, turn, and maneuver in a space smaller than its actual size, like a car in a crowded parking lot. More energy is required to break bonds and permit flow in liquids composed of molecules that are associated through hydrogen bonds. These bonds are broken at higher temperatures by thermal movement, however, and E_a decreases markedly. Diffusion (see Chapter 13) is similar to viscosity flow and, like fluidity, the reciprocal of viscosity, the rate of diffusion increases exponentially with temperature.

Example 17-2. The modified Arrhenius equation 17-5, is used to obtain the dependence of viscosity of liquids on temperature. Use equation (17-5) and the viscosity versus temperature data for glycerin (Table 17-2) to obtain the constant A , and E_a , (the activation energy to initiate flow). What is the value of r^2 , the square of the correlation coefficient?

Equation (17-5) is written in logarithmic form

$$\ln \eta = \ln A + \frac{E_a}{R} \frac{1}{T} \quad (17-6)$$

According to equation (17-6), a regression of $\ln \eta$ against $1/T$ gives E_a from the slope and in A from the intercept. Using the values given in Table 17-2, the equation is

$$\ln \eta = -23.4706 + 9012 \frac{1}{T}$$

Slope = 9012 = E_a/R ; E_a = 9012 \times 1.9872 = 17,909 cal/mole

Intercept = -23.4706 = $\ln A$; A = 6.40985 \times 10⁻¹¹; r^2 = 0.997

NON-NEWTONIAN SYSTEMS

The pharmacist probably deals more frequently with non-Newtonian materials than with simple liquids, and should therefore have suitable methods for the study of these complex substances. *Non-Newtonian bodies* are those substances that fail to follow Newton's equation of flow; liquid and solid heterogeneous dispersions such as colloidal solutions, emulsions, liquid suspensions, ointments, and similar products make up this class. When non-Newtonian materials are analyzed in a rotational viscometer (see pp. 463-466) and the results are plotted, various consistency curves, representing three classes of flow, are recognized: *plastic*, *pseudo-plastic*, and *dilatant*.

Plastic Flow. In Figure 17-2b, the curve represents a body that exhibits plastic flow; such materials are known as *Bingham bodies* in honor of the pioneer of modern rheology and the first investigator to study plastic substances in a systematic manner.

The plastic flow curve does not pass through the origin but rather intersects the shearing stress axis (or will if the straight part of the curve is extrapolated to the axis) at a particular point referred to as the *yield*

TABLE 17-1. Absolute Viscosity of Some Newtonian Liquids at 20° C

Liquid	Viscosity (cps)
Castor oil	1000
Chloroform	0.563
Ethyl alcohol	1.19
Glycerin, 93%	400
Olive oil	100
Water	1.0019

TABLE 17-2. Viscosity of Glycerin at Several Temperatures*

Temp. °C	-42	-20	0	6	15	20	25	30
Temp. °K	231	253	273	279	288	293	298	303
1/T (°K ⁻¹)	0.00432	0.00395	0.00366	0.00358	0.00347	0.00341	0.00336	0.00330
η , cp	6.71×10^6	1.34×10^5	12110	6260	2330	1490	954	629
$\ln \eta$	15.719	11.806	9.402	8.742	7.754	7.307	6.861	6.444

*Data from CRC Handbook of Chemistry and Physics, 3rd Edition, CRC Press, Boca Raton, Fla., 1982, p. F-44.

value. A Bingham body does not begin to flow until a shearing stress, corresponding to the yield value, is exceeded. At stresses below the yield value, the substance acts as an elastic material. The rheologist classifies Bingham bodies, that is, those substances that exhibit a yield value, as solids, whereas substances that begin to flow at the smallest shearing stress and show no yield value are defined as liquids. Yield value is an important property of certain dispersions.

The slope of the rheogram in Figure 17-2b is termed *mobility*, analogous to fluidity in Newtonian systems, and its reciprocal is known as the *plastic viscosity*, U . The equation describing plastic flow is

$$U = \frac{(F - f)}{G} \quad (17-7)$$

in which f is the yield value, or intercept, on the shear stress axis in dynes cm^{-2} , and F and G are as previously defined.

Example 17-3. A plastic material was found to have a yield value of 5200 dynes cm^{-2} . At shearing stresses above the yield value, F was found to increase linearly with G . If the rate of shear was 150 sec^{-1} when F was 8000 dynes cm^{-2} , calculate U , the plastic viscosity of the sample.

Substituting into equation (17-7):

$$\begin{aligned} U &= (8000 - 5200)/150 \\ &= 2800/150 \\ &= 18.67 \text{ poise.} \end{aligned}$$

Plastic flow is associated with the presence of flocculated particles in concentrated suspensions. As a result, a continuous structure is set up throughout the system. The yield value is present because of the contacts between adjacent particles (brought about by van der Waals forces), which must be broken down before flow can occur. Consequently, the yield value is an indication of the force of flocculation: the more flocculated the suspension, the higher will be the yield value. Frictional forces between moving particles can also contribute to the yield value. As was shown in Example 17-3, once the yield value has been exceeded, any further increase in shearing stress (i.e., $F - f$) brings about a directly proportional increase in G , the rate of shear. In effect, a plastic system resembles a Newtonian system at shear stresses above the yield value.

Pseudoplastic Flow. A large number of pharmaceutical products, including natural and synthetic gums, for example, liquid dispersions of tragacanth, sodium alginate, methylcellulose, and sodium carboxymethylcellulose, exhibit *pseudoplastic flow*. As a general rule,

pseudoplastic flow is exhibited by polymers in solution, in contrast to plastic systems, which are composed of flocculated particles in suspension. As seen in Figure 17-2c the consistency curve for a pseudoplastic material begins at the origin (or at least approaches it at low rates of shear). Consequently, in contrast to Bingham bodies, there is no yield value. Since, however, no part of the curve is linear, one cannot express the viscosity of a pseudoplastic material by any single value.

The viscosity of a pseudoplastic substance decreases with increasing rate of shear. An apparent viscosity may be obtained at any rate of shear from the slope of the tangent to the curve at the specified point. The most satisfactory representation for a pseudoplastic material at the present time, however, is probably a graphic plot of the entire consistency curve.

The curved rheogram for pseudoplastic materials results from a shearing action on the long-chain molecules of materials such as linear polymers. As the shearing stress is increased, the normally disarranged molecules begin to align their long axes in the direction of flow. This orientation reduces the internal resistance of the material and allows a greater rate of shear at each successive shearing stress. In addition, some of the solvent associated with the molecules may be released, resulting in an effective lowering of the concentration and the size of the dispersed molecules. This, too, will effect a lowering of the apparent viscosity.

Obviously, objective comparisons between different pseudoplastic systems are more difficult than with either Newtonian or plastic systems. Thus, a Newtonian system is completely described by η , the viscosity. A system exhibiting plastic flow is adequately described by the yield value and the plastic viscosity. Accordingly, several approaches have been used to obtain meaningful parameters that will allow different pseudoplastic materials to be compared. Of those discussed by Martin et al.,³ the exponential formula

$$F^N = \eta' G \quad (17-8)$$

has been used most frequently for pseudoplastics. The exponent N rises as the flow becomes increasingly non-Newtonian. When $N = 1$, equation (17-8) reduces to equation (17-2) and the flow is Newtonian. The term η' is a viscosity coefficient. Following rearrangement, equation (17-8) may be written in the logarithmic form:

$$\log G = N \log F - \log \eta' \quad (17-9)$$

This is an equation for a straight line. Many pseudoplastic systems fit this equation when $\log G$ is plotted as a function of $\log F$.⁴ Several of the more important pseudoplastic suspending agents used in pharmacy, however, do not conform to equation (17-9).⁵ Modified equations have been suggested by Shangraw et al. and by Casson and Patton.⁶ An analog computer has been used to characterize pseudoplastic systems, based on the assumption that the typical rheogram of a pseudoplastic substance is composed of a first-order segment and a zero-order segment.⁷

Dilatant Flow. Certain suspensions with a high percentage of dispersed solids exhibit an increase in resistance to flow with increasing rates of shear. Such systems actually increase in volume when sheared and are hence termed *dilatant*; their flow properties are illustrated by Figure 17-2d. It should be immediately obvious that this type of flow is the inverse of that possessed by pseudoplastic systems. Whereas pseudoplastic materials are frequently referred to as "shear-thinning systems," dilatant materials are often termed "shear-thickening systems." When the stress is removed, a dilatant system returns to its original state of fluidity.

Equation (17-8) can be used to describe dilatancy in quantitative terms. In this case, N is always less than 1 and decreases as the degree of dilatancy increases. As N approaches 1, the system becomes increasingly Newtonian in behavior.

Substances possessing dilatant flow properties are invariably suspensions containing a high concentration (about 50% or greater) of small, deflocculated particles. As discussed previously, particulate systems of this type that are flocculated would be expected to possess plastic, rather than dilatant, flow characteristics. Dilatant behavior may be explained as follows. At rest, the particles are closely packed with the interparticle volume, or voids, being at a minimum. The amount of vehicle in the suspension is sufficient, however, to fill this volume and permits the particles to move relative to one another at low rates of shear. Thus, one may pour a dilatant suspension from a bottle since under

these conditions it is reasonably fluid. As the shear stress is increased, the bulk of the system expands or dilates; hence the term *dilatant*. The particles, in an attempt to move quickly past each other, take on an open form of packing, as depicted in Figure 17-3. Such an arrangement leads to a significant increase in the interparticle void volume. The amount of vehicle remains constant and, at some point, becomes insufficient to fill the increased voids between the particles. Accordingly, the resistance to flow increases because the particles are no longer completely wetted, or lubricated, by the vehicle. Eventually, the suspension will set up as a firm paste. Behavior of this nature necessitates that great care be taken in processing dilatant materials. Conventionally, the processing of dispersions containing solid particles is facilitated by the use of high-speed mixers, blenders, or mills. Although this is advantageous with all other rheologic systems, dilatant materials may solidify under these conditions of high shear, thereby overloading and damaging the processing equipment.

THIXOTROPY

Previously the reader was introduced to the several types of behavior observed when the rate of shear was progressively increased and plotted against the resultant shear stress. It was tacitly assumed that if the rate of shear was reduced once the desired maximum rate had been reached, the down-curve would be identical with and superimposed on the up-curve. While this is so with Newtonian systems, the down-curve for non-Newtonian systems can be displaced with regard to the up-curve. With shear-thinning systems (i.e., pseudoplastic), the down-curve is frequently displaced to the left of the up-curve (as in Fig. 17-4), showing that the material has a lower consistency at any one rate of shear on the down-curve than it had on the up-curve. This indicates a breakdown of structure (and hence shear thinning) that does not reform immediately when the stress is removed or reduced. This phenomenon,

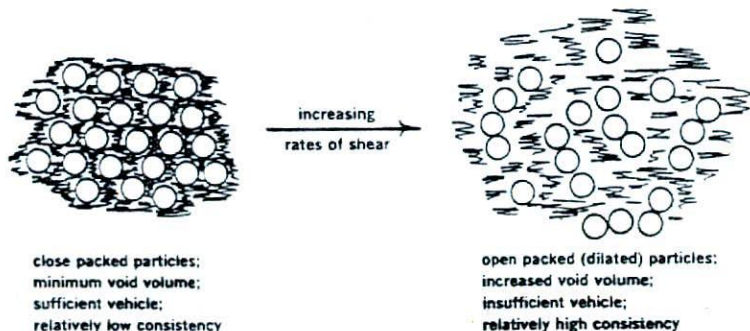


Fig. 17-3. Explanation of dilatant flow behavior.

known as *thixotropy*, may be defined⁸ as "an isothermal and comparatively slow recovery, on standing of a material, of a consistency lost through shearing." As so defined, thixotropy may be applied only to shear-thinning systems. Typical rheograms for plastic and pseudoplastic systems exhibiting this behavior are shown in Figure 17-4.

Thixotropic systems usually contain asymmetric particles that, through numerous points of contact, set up a loose three-dimensional network throughout the sample. At rest, this structure confers some degree of rigidity on the system, and it resembles a gel. As shear is applied and flow starts, this structure begins to break down as the points of contact are disrupted and the particles become aligned. The material undergoes a gel-to-sol transformation and exhibits shear thinning. Upon removal of the stress, the structure starts to reform. This process is not instantaneous; rather, it is a progressive restoration of consistency as the asymmetric particles come into contact with one another by undergoing random Brownian movement. The rheograms obtained with thixotropic materials are therefore highly dependent on the rate at which shear is increased or decreased and the length of time a sample is subjected to any one rate of shear. In other words, the previous history of the sample has a significant effect on the rheologic properties of a thixotropic system. For example, suppose that in Figure 17-5 the shear rate of a thixotropic material is increased in a constant manner from *a* to point *b* and is then decreased at the same rate back to *e*. Typically, this would result in the so-called hysteresis loop *abe*. If, however, the sample was taken to point *b* and the shear rate held constant for a certain period of time (say, t_1 seconds), the shearing stress; and hence the consistency, would decrease to an extent depending on the time of shear, the rate of shear, and the degree of structure in the sample. Decreasing the shear rate would then result in the *hysteresis loop*, *abc*. If the sample had been held at the same rate of shear for t_2 seconds, the loop *abcde* would have been observed. Obviously, therefore, the rheogram of a thixotropic material is not unique but will depend on the rheologic history of the sample and the approach used in obtaining the rheogram. This is an important point to

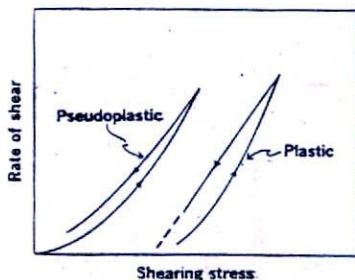


Fig. 17-4. Thixotropy in plastic and pseudoplastic flow systems.

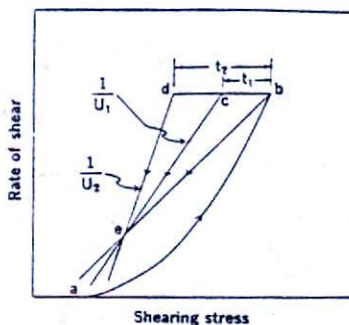


Fig. 17-5. Structural breakdown with time of a plastic system possessing thixotropy when subjected to a constant rate of shear for t_1 and t_2 seconds. See text for discussion.

bear in mind when attempting to obtain a quantitative measure of thixotropy. This will become apparent in the subsequent section.

Measurement of Thixotropy. A quantitative measurement of thixotropy can be attempted in several ways. The most apparent characteristic of a thixotropic system is the hysteresis loop, formed by the up- and down-curves of the rheogram. This *area of hysteresis* has been proposed as a measure of thixotropic breakdown; it may be obtained readily by means of a planimeter or other suitable technique.

With plastic (Bingham) bodies, two approaches are frequently used to estimate the degree of thixotropy. The first is to determine the structural breakdown with time at a *constant* rate of shear. The type of rheogram needed for this estimation is shown in Figure 17-5; the steps necessary to obtain it have already been described. Based on such a rheogram, a thixotropic coefficient *B*, the rate of breakdown with time at constant shear rate, is calculated as follows:

$$B = \frac{U_1 - U_2}{\ln \frac{t_2}{t_1}} \quad (17-10)$$

in which U_1 and U_2 are the plastic viscosities of the two down-curves, calculated from equation (17-7), after shearing at a constant rate for t_1 and t_2 seconds, respectively. The choice of shear rate is arbitrary. A more meaningful, though time-consuming, method for characterizing thixotropic behavior is to measure the fall in stress with time several rates of shear.

The second approach is to determine the structural breakdown due to *increasing* shear rate. The principle involved in this approach is shown in Figure 17-6, in which two hysteresis loops are obtained having different maximum rates of shear, v_1 and v_2 . In this case, a thixotropic coefficient *M*, the loss in shearing stress per unit increase in shear rate, is obtained from

$$M = \frac{(U_1 - U_2)}{\ln (v_2/v_1)} \quad (17-11)$$

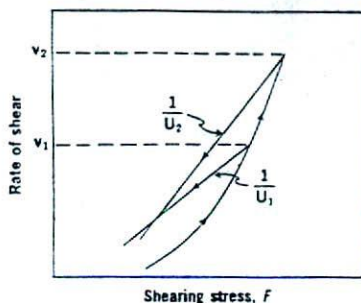


Fig. 17-6. Structural breakdown of a plastic system possessing thixotropy when subjected to increasing shear rates. See text for discussion.

in which M is in dynes sec/cm² and U_1 and U_2 are the plastic viscosities for two separate down-curves having maximum shearing rates of v_1 and v_2 , respectively. A criticism of this technique is that the two rates of shear, v_1 and v_2 , are chosen arbitrarily; the value of M will depend on the rate of shear chosen since these shear rates will affect the down-curves and hence the values of U that are calculated.

Bulges and Spurs. Dispersions employed in pharmacy may yield complex hysteresis loops when sheared in a viscometer in which shear rate (rather than shear stress) is increased to a point, then decreased, and the shear stress is read at each shear rate value to yield appropriate rheograms. Two such complex structures are shown in Figures 17-7 and 17-8. A concentrated aqueous bentonite gel, 10 to 15% by weight, produces a hysteresis loop with a characteristic *bulge* in the up-curve. It is presumed that the crystalline plates of bentonite form a "house-of-cards structure" that causes the swelling of bentonite magmas. This three-dimensional structure results in a bulged hysteresis loop as observed in Figure 17-7. In still more highly struc-

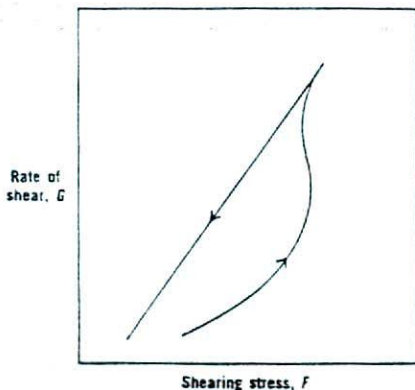


Fig. 17-7. Rheogram of a thixotropic material showing a bulge in the hysteresis loop.

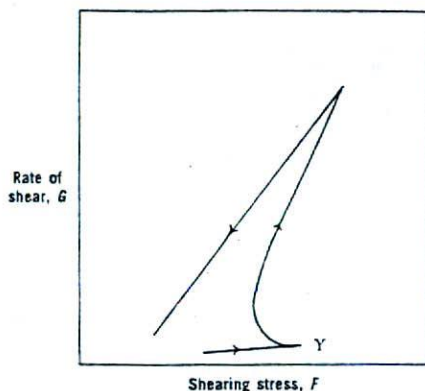


Fig. 17-8. Rheogram of a thixotropic material showing a spur value Y in the hysteresis loop.

tured systems, such as a procaine penicillin gel formulated by Ober et al.⁹ for intramuscular injection, the bulged curve may actually develop into a spur-like protrusion (Fig. 17-8). The structure demonstrates a high yield or *spur value*, Y , that traces out a bowed up-curve when the three-dimensional structure breaks in the viscometer, as observed in Figure 17-8. The spur value represents a sharp point of structural breakdown at low shear rate. It is difficult to produce the spur, and it may not be observed unless a sample of the gel is allowed to age undisturbed in the cup and bob assembly for some time before the rheologic run is made. The spur value is obtained by using an instrument in which the rate of shear can be slowly and uniformly increased, preferably automatically, and the shear stress read out or plotted on an X - Y recorder as a function of shear rate. Ober et al.⁹ found that penicillin gels having definite Y values were very thixotropic, forming intramuscular depots upon injection that afforded prolonged blood levels of the drug.

Negative Thixotropy. From time to time in the measurement of supposedly thixotropic materials, one observes a phenomenon called *negative thixotropy* or *antithixotropy*, which represents an increase rather than a decrease in consistency on the down-curve. This increase in thickness or resistance to flow with increased time of shear was observed by Chong et al.¹⁰ in the rheologic analysis of magnesia magma. It was detected at shear rates of greater than 30 sec⁻¹; below 30 sec⁻¹ the magma showed normal thixotropy, the down-curve appearing to the left of the up-curve. As pointed out by Chong et al., antithixotropy had been reported by other investigators, but not in pharmaceutical systems.

It was observed that when magnesia magma was alternately sheared at increasing and then decreasing rates of shear, the magma continuously thickened (an increase in shearing stress per unit shear rate) but at a decreasing rate, and it finally reached an equilibrium

state in which further cycles of increasing-decreasing shear rates no longer increased the consistency of the material. The antithixotropic character of magnesia magma is demonstrated in Figure 17-9. The equilibrium system was found to be gel-like and to provide great suspendability, yet it was readily pourable. When allowed to stand, however, the material returned to its sol-like properties.

Antithixotropy or negative thixotropy should not be confused with dilatancy or rheopecty. Dilatant systems are deflocculated and ordinarily contain greater than 50% by volume of solid dispersed phase, whereas antithixotropic systems have low solids content (1 to 10%) and are flocculated, according to Samyn and Jung.¹¹ *Rheopecty* is a phenomenon in which a solid forms a gel more readily when gently shaken or otherwise sheared than when allowed to form the gel while the material is kept at rest.¹² In a rheopectic system, the gel is the equilibrium form, whereas in antithixotropy, the equilibrium state is the sol. Samyn and Jung note that magnesia magma and clay suspensions may show a negative rheopecty, analogous to negative thixotropy. It is believed that antithixotropy results from an increased collision frequency of dispersed particles or polymer molecules in suspension, resulting in increased interparticle bonding with time. This changes the original state consisting of a large number of individual particles and small flocules to an eventual equilibrium state consisting of a small number of relatively large flocules. At rest, the large flocules break up and gradually return to the original state of small flocules and individual particles.

As more rheologic studies are done with pharmaceuticals, negative thixotropy no doubt will be observed in other materials.

Thixotropy in Formulation. Thixotropy is a desirable property in liquid pharmaceutical systems that ideally

should have a high consistency in the container, yet pour or spread easily. For example, a well-formulated thixotropic suspension will not settle out readily in the container, will become fluid on shaking, and will remain long enough for a dose to be dispensed. Finally, it will regain consistency rapidly enough so as to maintain the particles in a suspended state. A similar pattern of behavior is desirable with emulsions, lotions, creams, ointments, and parenteral suspensions to be used for intramuscular depot therapy.

With regard to suspension stability, there is a relationship between the degree of thixotropy and the rate of sedimentation; the greater the thixotropy, the lower the rate of settling. Concentrated parenteral suspensions containing from 40 to 70% w/v of procaine penicillin G in water were found to have a high inherent thixotropy and were shear-thinning.¹³ Consequently, breakdown of the structure occurred when the suspension was caused to pass through the hypodermic needle. The consistency was then recovered as the rheologic structure reformed. This led to the formation of a depot of drug at the site of injection in the muscle, from which drug was slowly removed and made available to the body. The degree of thixotropy was shown to be related to the specific surface of the penicillin used.

The reader should also appreciate that the degree of thixotropy may change over time and result in an inadequate formulation. Thixotropic systems are complex, and it is unrealistic to expect that rheologic changes can be meaningfully followed by the use of one parameter. Thus, in a study concerned with the aging effects of thixotropic clay, Levy¹⁴ found it necessary to follow changes in plastic viscosity, area of hysteresis, yield value, and spur value.

DETERMINATION OF RHEOLOGIC PROPERTIES

Choice of Viscometer. The successful determination and evaluation of the rheologic properties of a particular system depend, in large part, on choosing the correct instrumental method. Since the rate of shear in a Newtonian system is directly proportional to the shearing stress, one can use instruments that operate at a single rate of shear. These "one-point" instruments provide a single point on the rheogram; extrapolation of a line through this point to the origin will result in a complete rheogram. Implicit in the use of a "one-point" instrument is the prior knowledge that the flow characteristics of the material are Newtonian. Unfortunately, this is not always the case, and should the system be non-Newtonian, a "one-point" determination is virtually useless in characterizing the flow properties of the system. It is therefore essential that, with non-Newtonian systems, the instrumentation used be able to operate at a variety of rates of shear. Only by the use of "multipoint" instruments is it possible to obtain the complete rheogram for those systems. The use of a "one-point" instrument, even as a quality

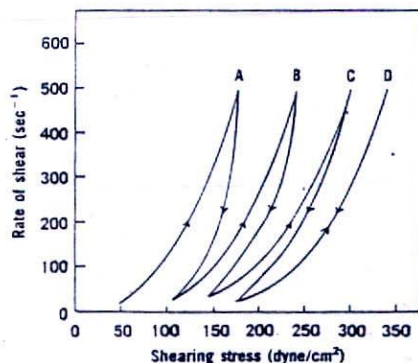


Fig. 17-9. Rheogram of magnesia magma showing antithixotropic behavior. The material is sheared at repeated increasing and then decreasing rates of shear. At stage D, further cycling no longer increased the consistency, and the up- and down-curves coincided. (From C. W. Chong, S. P. Eriksen, and J. W. Swintosky, *J. Am. Pharm. Assoc., Sci. Ed.* 49, 547, 1960, reproduced with permission of the publisher.)

control in industry, is erroneous if the system is non-Newtonian since, as illustrated in Figure 17-10, the flow properties could vary significantly, yet will appear to be unchanged.

The important conclusion, therefore, is that while all viscometers can be used to determine the viscosity of Newtonian systems, only those with variable shear-stress controls can be used for non-Newtonian materials.

Other rheologic properties such as tackiness or stickiness, "body," "slip," and "spreadability" are difficult to measure by means of conventional apparatus and, in fact, do not have precise meanings. The individual factors, however—viscosity, yield value, thixotropy, and the other properties that contribute to the total consistency of non-Newtonian pharmaceuticals—can be analyzed to some degree of satisfaction in reliable apparatus. An attempt must be made to express these properties in meaningful terms if rheology is to aid in the development, production, and control of pharmaceutical preparations.

The many types of viscometers have been discussed in detail by Hatschek,¹⁵ Martin et al.,³ Sherman,¹⁶ and Van Wazer et al.¹⁷ The present discussion will be limited to four instruments, namely the capillary, falling sphere, cup and bob, and cone and plate viscometers. The first two are for use only with Newtonian materials, while the latter two may be used with both types of flow system.

Pseudoplastic materials should be studied with an instrument that is capable of a wide range of shearing

rates. The results can then be used to represent the viscosity of a suspending agent at rest, that is, at a negligible rate of shear, and while being agitated, poured from a bottle, or applied to the skin at moderately high rates of shear. Capillary and falling ball viscometers, operating at a single rate of shear, are unable to describe these changes. Even rotational instruments, unless properly designed, will not give satisfactory results.

Capillary Viscometer. The viscosity of a Newtonian liquid may be determined by measuring the time required for the liquid to pass between two marks as it flows by gravity through a vertical capillary tube, known as an *Ostwald viscometer*. A modern adaptation of the original Ostwald viscometer is shown in Figure 17-11. The time of flow of the liquid under test is compared with the time required for a liquid of known viscosity (usually water) to pass between the two marks. If η_1 and η_2 are the viscosities of the unknown and the standard liquids, ρ_1 and ρ_2 are the densities of the liquids, and t_1 and t_2 are the respective flow times in seconds, the absolute viscosity of the unknown liquid, η_1 , is determined by substituting the experimental values in the equation

$$\frac{\eta_1}{\eta_2} = \frac{\rho_1 t_1}{\rho_2 t_2} \quad (17-12)$$

The value $\eta_1/\eta_2 = \eta_{rel}$ is known as the *relative viscosity* of the liquid under test.

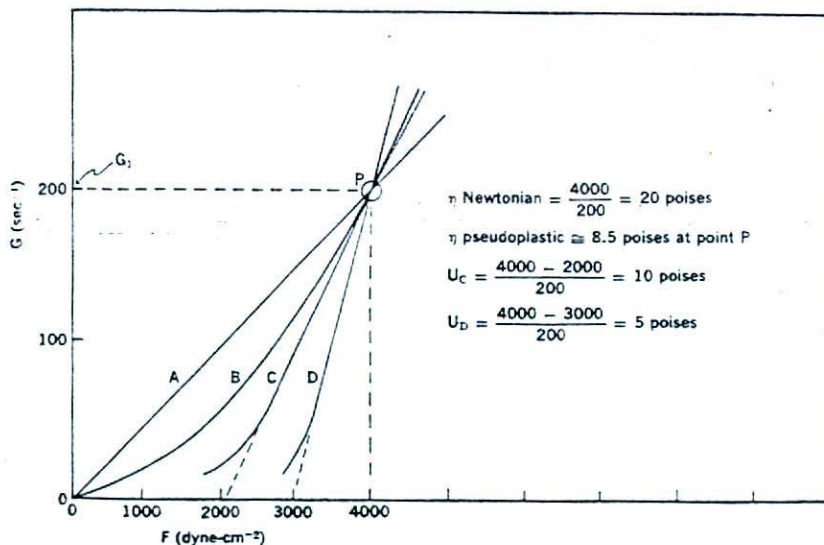


Fig. 17-10. Illustration of errors inherent in the use of a "one-point" instrument for non-Newtonian systems. Regardless of the fact that A is Newtonian, B is pseudoplastic, and C and D are two different plastic systems, a "one-point" instrument could indicate a common viscosity of 20 poises ($F = 4000$ dynes cm^{-2} and $G = 200$ sec^{-1}). Use of a "one-point" instrument is proper only in the case of the Newtonian systems. (From A. Martin, G. S. Banker, and A. H. C. Chun, in *Advances in Pharmaceutical Sciences*, H. S. Bean, A. H. Beckett and J. E. Carless, Eds., Academic Press, London, 1964, Chapter 1, reproduced with permission of the copyright owner.)

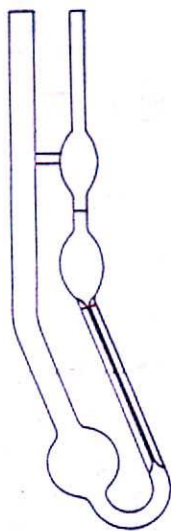


Fig. 17-11. Ostwald-Cannon-Fenske viscometer.

Example 17-4. Consider the viscosity measurement of acetone discussed in *Example 17-1*. Assume that the time required for acetone to flow between the two marks on the capillary viscometer was 45 seconds, and for water the time was 100 seconds at 25° C. The density of acetone is 0.786 g/cm³ and that of water is 0.997 g/cm³ at 25° C. The viscosity of water is 0.8904 centipoise at this temperature. The viscosity of acetone at 25° C may be calculated using equation (17-12):

$$\frac{\eta_1}{0.8904} = \frac{0.786 \times 45.0}{0.997 \times 100}$$

$$\eta_1 = 0.316 \text{ cp}$$

Equation (17-12) is based on *Poiseuille's law* for a liquid flowing through a capillary tube,

$$\eta = \frac{\pi r^4 t \Delta P}{8lV} \quad (17-13)$$

in which r is the radius of the inside of the capillary, t is the time of flow, ΔP is the pressure head in dyne/cm² under which the liquid flows, l is the length of the capillary, and V is the volume of liquid flowing. Equation (17-12) is obtained from Poiseuille's law (equation (17-13)) as follows. The radius, length, and volume of a given capillary viscometer are invariants and may be combined into a constant, K . Equation (17-13) may then be written

$$\eta = Kt \Delta P \quad (17-14)$$

The pressure head ΔP depends on the density ρ of the liquid being measured, the acceleration of gravity, and the difference in heights of the liquid levels in the two arms of the viscometer. The acceleration of gravity is a constant, however; and if the levels in the capillary are

kept constant for all liquids, we can incorporate these terms in the constant and write for the viscosities of the unknown and the standard liquids:

$$\eta_1 = K't_1\rho_1 \quad (17-15)$$

$$\eta_2 = K't_2\rho_2 \quad (17-16)$$

Therefore, when the flow periods for two liquids are compared in the same capillary viscometer, the division of (17-15) by (17-16) gives equation (17-12). The U.S. Pharmacopeia XXII, p. 1619, suggested a capillary apparatus for determining the viscosity of high-viscosity types of methylcellulose solutions.

Example 17-5. The Poiseuille equation may be used to calculate the pressure difference in the arteries and capillaries: Figure 17-12 depicts blood circulation in the body.¹⁶ The systolic pressure is normally about 120 mm Hg and the diastolic pressure about 80 mm Hg. Therefore, at rest the average blood pressure is about 100 mm Hg.

The Poiseuille equation (17-13) may be written

$$r = \left(\frac{8\eta l(V/t)}{\pi \Delta P} \right)^{1/4}$$

in which the viscosity, η , of the blood at normal body temperature is 4 cps or 0.04 poise = 0.04 dyne sec cm⁻², and l is the distance, say 1 cm, along an artery. The average rate of blood flow V/t at rest is 80 cm³ sec⁻¹, and the pressure drop ΔP over a distance of 1 cm along the artery is 3.8 mm Hg (1 dyne cm⁻² = 7.5 × 10⁻⁴ mm Hg). Calculate

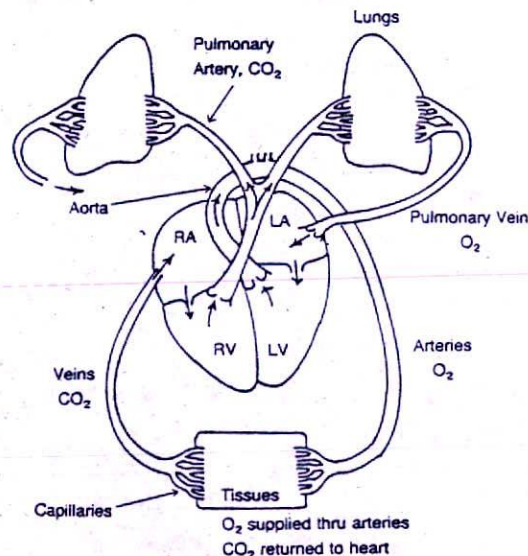


Fig. 17-12. Blood flow through the heart, lungs, arteries, veins, and capillaries. Blood with oxygen bound to hemoglobin is pumped through the left ventricle, LV, of the heart to the arteries and is released in the tissues. Carbon dioxide is taken up by the venous blood and is pumped to the right ventricle, RV, of the heart by way of the right atrium, RA. The blood then passes to the lungs, where carbon dioxide is released and oxygen is taken up. The blood, now rich in oxygen, passes from the lungs to the left atrium, LA, and through the left ventricle, LV, to complete the cycle. See problems 17-15, 17-16, and 17-17 involving the viscosity of flowing blood.

the radius r in cm of the artery. In the following equation, "s" stands for seconds.

$$r \text{ (cm)} = \left(\frac{8(0.04 \text{ dyne s cm}^{-2})(1 \text{ cm})(80 \text{ cm}^3 \text{ s}^{-1})}{\pi(3.8 \text{ mm Hg}) \times (1 \text{ dyne cm}^{-2}/7.50 \times 10^{-4} \text{ mm Hg})} \right)^{1/4}$$

The radius in cm = $(0.00505 \text{ cm})^{1/4} = 0.27 \text{ cm}$.

Falling Sphere Viscometer. In this type of viscometer, a glass or steel ball rolls down an almost vertical glass tube containing the test liquid at a known constant temperature. The rate at which a ball of a particular density and diameter falls is an inverse function of the viscosity of the sample. The Høepler viscometer, shown in Figure 17-13, is a commercial instrument based on this principle. The sample and ball are placed in the inner glass tube and allowed to reach temperature equilibrium with the water in the surrounding constant-temperature jacket. The tube and jacket are then inverted, which effectively places the ball at the top of the inner glass tube. The time for the ball to fall between two marks is accurately measured and repeated several times. The viscosity of a Newtonian liquid is then calculated from

$$\eta = t(S_b - S_f)B \quad (17-17)$$

in which t is the time interval in seconds for the ball to fall between the two points, and S_b and S_f are the specific gravities of the ball and fluid under examination at the temperature being used. B is a constant for a particular ball and is supplied by the manufacturer. Since a variety of glass and steel balls of different diameters are available, this instrument can be used over the range 0.5 to 200,000 poise. For best results, a ball should be used such that t is not less than 30 seconds.

Cup and Bob Viscometer. In cup and bob viscometers, the sample is sheared in the space between the outer wall of a bob and the inner wall of a cup into which the bob fits. The principle is illustrated in Figure 17-14. The various instruments available differ mainly in whether the torque set up in the bob results from the cup or from the bob being caused to revolve. In the

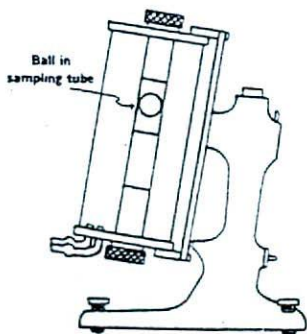


Fig. 17-13. Høepler falling ball viscometer.

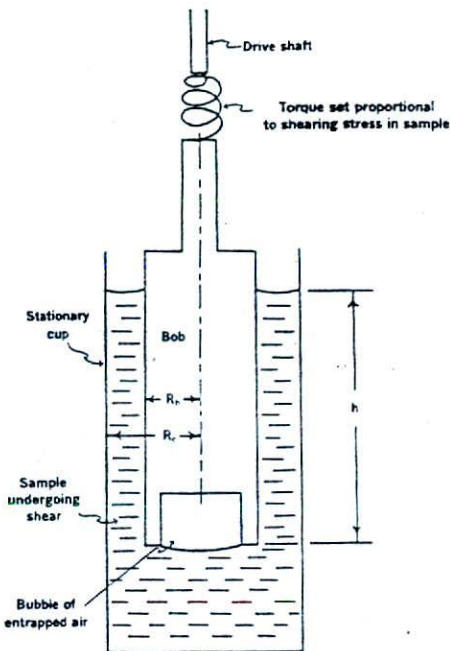


Fig. 17-14. Principle of rotational cup and bob viscometer (Searle type). See text for explanation.

Couette type of viscometer, the cup is rotated. The viscous drag on the bob due to the sample causes it to turn. The resultant torque is proportional to the viscosity of the sample. The MacMichael viscometer is an example of such an instrument. The *Searle* type of viscometer involves the principle of a stationary cup and a rotating bob. The torque resulting from the viscous drag of the system under examination is generally measured by a spring or sensor in the drive to the bob. The Rotovisco viscometer, shown in Figure 17-15, is an example of this type; it can also be modified to operate as a cone and plate instrument.

Example 17-6. The Haake Rotovisco apparatus uses interchangeable measuring heads, MK-50 and MK-500. The shear stress, F , in dyne/cm^2 is obtained from a dial reading S and is calculated using the formula

$$F(\text{dyne/cm}^2) = K_F \cdot S \quad (17-18)$$

where K_F is a shear stress factor.

The shear rate, G , in sec^{-1} , is proportional to the adjustable speed, n , in revolutions per minute, of the rotating cylinder in the cup containing the sample. The formula for shear rate is

$$G \text{ (sec}^{-1}\text{)} = K_G \cdot n \quad (17-19)$$

where K_G is a shear rate factor that varies with the particular rotating cylinder used. Three cups and cylinders (sensor systems) are supplied with the instrument, MV1, MV11, and MV111. For the measuring head MK-50 and the sensor system MV1, the values for the constants K_F and K_G are $K_F = 2.95 \text{ dyne/cm}^2$ and $K_G = 2.35 \text{ min/sec}$.

In the analysis of a solution of a new glucose derivative, which is found to be Newtonian, the following data were obtained in a typical

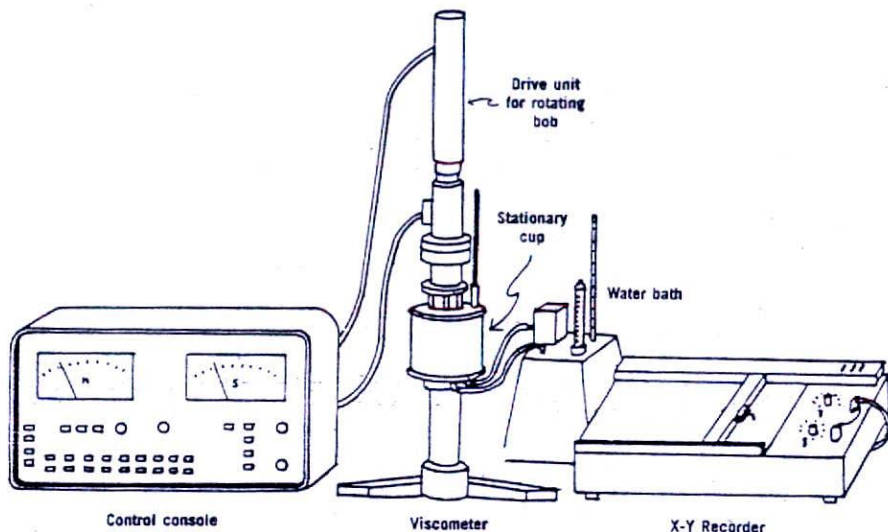


Fig. 17-15. Haake Rotovisco viscometer. The rate of shear G is selected manually or programmed for automatic plotting of up- and down-curves. Its value in sec^{-1} is proportional to the speed of the bob shaft, dialed in and read as n on the console. The shear stress is read on the scale S or obtained from the rheogram, plotted on the X - Y recorder.

experimental run at 25°C using the Haake viscometer with the MK-50 head and MVI sensor system. With the cylinder rotating at 180 rpm, the dial reading S was obtained as 65.5 scale divisions.¹⁹ Calculate the Newtonian viscosity of the new glucose derivative. What are the values of shear stress, F , and the rate of shear, G ?

Using equations (17-18) and (17-19),

$$F = 2.95 \times 65.5 = 193.2 \text{ dyne/cm}^2$$

$$G = 2.35 \times 180 = 423.0 \text{ sec}^{-1}$$

Now, the Newtonian viscosity is readily obtained as

$$\eta = \frac{F}{G} = \frac{193.2}{423.0} = 0.457 \text{ poise, or } 45.7 \text{ cp}$$

A popular viscometer based on the Searle principle is the Stormer instrument. This viscometer, a modification of that described by Fischer,²⁰ is shown in Figure 17-16. In operation, the test system is placed in the space between the cup and the bob and allowed to reach temperature equilibrium. A weight is placed on the hanger, and the time for the bob to make 100 revolutions is recorded by the operator. This data is then converted to rpm. The weight is increased and the whole procedure repeated. In this way, a rheogram can be constructed by plotting rpm versus weight added. By the use of appropriate constants, the rpm values can be converted to actual rates of shear in sec^{-1} . Similarly, the weights added can be transposed into the units of shear stress, namely, dyne cm^{-2} . According to Araujo,²¹ the Stormer instrument should not be used with systems having a viscosity below 20 cps.

It can be shown that, for a rotational viscometer, equation (17-1) becomes

$$\Omega = \frac{1}{\eta} \frac{T}{4\pi n} \left(\frac{1}{R_b^2} - \frac{1}{R_c^2} \right) \quad (17-20)$$

in which Ω is the angular velocity in radians sec^{-1} produced by T , the torque in dynes cm. The depth to which the bob is immersed in the liquids is h , while R_b and R_c are the radii of the bob and cup, respectively (see Fig. 17-14). The viscous drag of the sample on the base of the bob is not taken into account by equation (17-20). Either an "end correction" must be applied or, more usually, the base of the bob is recessed, as shown in Figure 17-14. In this case, a pocket of air is entrapped between the sample and the base of the bob, rendering the contribution from the base of the bob negligible. It is frequently more convenient to combine

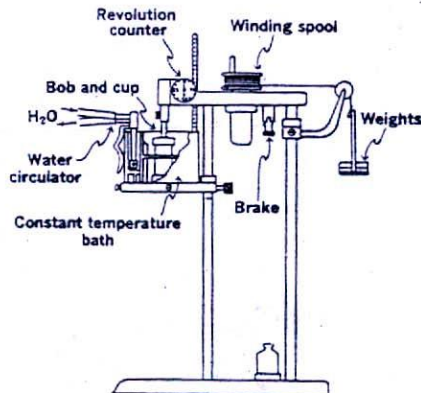


Fig. 17-16. Stormer viscometer: The falling weights cause the bob to rotate in the stationary cup. The velocity of the bob is obtained by means of a stop watch and the revolution counter.

all the constants in equation (17-20), with the result that

$$\eta = K_v \frac{T}{\Omega} \quad (17-21)$$

in which K_v is a constant for the instrument. With the modified Stormer viscometer, Ω is a function of v , the rpm generated by the weight w , in grams, that is proportional to T . Equation (17-21) may then be written as

$$\eta = K_v \frac{w}{v} \quad (17-22)$$

The constant K_v may be determined by analyzing an oil of known viscosity in the instrument; reference oils for this purpose are obtained from the National Bureau of Standards.

The equation for plastic viscosity when employing the Stormer viscometer is

$$U = K_v \frac{w - w_f}{v} \quad (17-23)$$

in which U is the plastic viscosity in poises, w_f is the yield value intercept in grams, and the other symbols have the meaning previously given in equation (17-22).

The yield value of a Bingham body is obtained by use of the expression

$$f = K_f \times w_f \quad (17-24)$$

in which K_f is equal to

$$K_f = \frac{2\pi}{60} \times \frac{1}{2.303 \log (R_c/R_b)}$$

in which R_c is the radius of the cup and R_b is the radius of the bob.

Example 17-7. A sample of a gel was analyzed in a modified Stormer viscometer (see Fig. 17-16). A driving weight w of 450 g produced a bob velocity v of 350 rpm. A series of velocities were obtained using other driving weights, and the data were plotted as shown in curve b of Figure 17-2. The yield value intercept w_f was obtained by extrapolating the curve to the shearing stress axis where $v = 0$, and the value of w_f was found to be 225 grams. The instrumental constant K_v is 52.0, and K_f is 20.0. What is the plastic viscosity and the yield value of the sample?

$$U = 52.0 \times \frac{450 - 225}{350} = 33.4 \text{ poises}$$

$$f = 20 \times 225 = 4500 \text{ dyne/cm}^2$$

The Brookfield Viscometer (Brookfield Engineering, Stoughton, Mass.) is a rotational viscometer of the Searle type that is popular in the quality-control laboratories of pharmaceutical manufacturers. A number of spindles (bobs) of various geometries, including cylinders, t-bars, and a cone-plate configuration, are available to provide scientific rheologic data for Newtonian and non-Newtonian liquids and for empirical viscosity measurements on pastes and other semisolid materials. Various models of the Brookfield Viscometer are available for high-, medium-, and low-viscosity

applications. Figure 17-17 depicts a cone-and-plate type of Brookfield viscometer. The cone-plate viscometer (the Ferranti-Shirley viscometer of Ferranti Ltd.) is described in some detail on pages 466-467.

Plug Flow. One potential disadvantage of the cup and bob viscometer is variable shear stress across the sample between the bob and the cup. We have seen that, in contrast to Newtonian systems, the apparent viscosity of non-Newtonian systems varies with shear stress. With plastic materials, the apparent viscosity below the yield value can be regarded as infinite. Above the yield value, the system possesses a finite viscosity U , the plastic viscosity. In a viscometer of the Searle type, the shear stress close to the rotating bob at relatively low rates of shear may be sufficiently high so as to exceed the yield value. The shear stress at the inner wall of the cup could (and frequently does), however, lie below the yield value. Material in this zone would therefore remain as a solid plug and the measured viscosity would be in error. A major factor determining whether or not *plug flow* occurs is the gap between the cup and the bob. The operator should always use the largest bob possible with a cup of a definite circumference so as to reduce the gap and minimize the chances of plug flow. In a system exhibiting plug flow in the viscometer, more and more of the sample is sheared at a stress above the yield value as

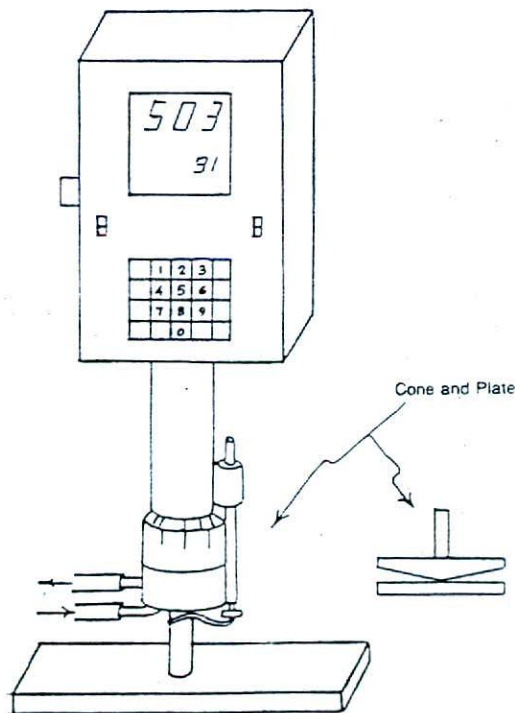


Fig. 17-17. A digital-type cone and plate viscometer, Brookfield.

the speed of rotation of the bob is increased. It is only when the shear stress at the wall of the cup exceeds the yield value, however, that the system as a whole undergoes laminar, rather than plug, flow, and the correct plastic viscosity is obtained.

The phenomenon of plug flow is important in the flow of pastes and concentrated suspensions through an orifice, for example, the extrusion of toothpaste from a tube. Thus, the high shear conditions along the inner circumference of the tube aperture cause a drop in consistency. This facilitates extrusion of the material in the core as a plug. This phenomenon is, however, undesirable when attempting to obtain the rheogram of a plastic system with a cup and bob viscometer. The next instrument to be discussed does not suffer from this drawback.

Cone and Plate Viscometer. The Ferranti-Shirley viscometer (Ferranti Ltd., England) is an example of a rotational cone and plate viscometer. The measuring unit of the apparatus is shown in Figure 17-18; the indicator unit and speed control amplifier are not shown. In operation, the sample is placed at the center of the plate, which is then raised into position under the cone, as shown in Figure 17-19.

The cone is driven by a variable-speed motor and the sample is sheared in the narrow gap between the stationary plate and the rotating cone. The rate of shear in revolutions per minute is increased and decreased by a selector dial and the viscous traction or torque (shearing stress) produced on the cone is read on the indicator scale. A plot of rpm or rate of shear versus

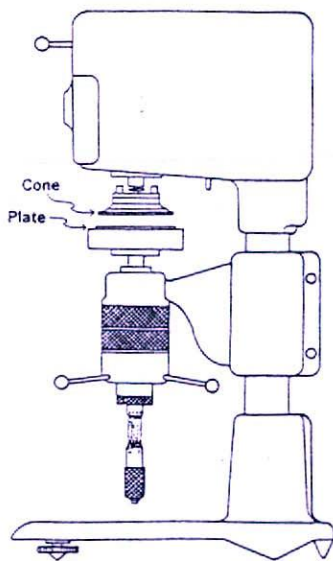


Fig. 17-18. The measuring unit of the Ferranti-Shirley cone-plate viscometer.

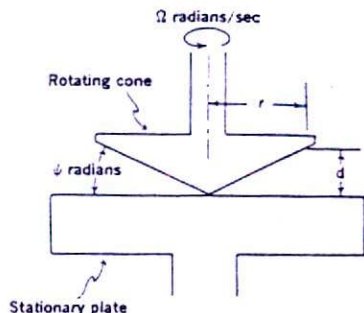


Fig. 17-19. Constant shear rate conditions in the cone and plate viscometer. The cone-to-plate angle, ψ , is greatly exaggerated here; it is ordinarily less than 1° (< 0.02 radians).

scale reading or shearing stress may thus be constructed in the ordinary manner.

The viscosity in poises of a Newtonian liquid measured in the cone-plate viscometer is calculated by use of the equation

$$\eta = C \frac{T}{v} \quad (17-25)$$

in which C is an instrumental constant, T is the torque reading, and v is the speed of the cone in revolutions per minute. For a material showing plastic flow, the plastic viscosity is given by the equation

$$U = C \frac{T - T_f}{v} \quad (17-26)$$

and the yield value is given by

$$f = C_f \times T_f \quad (17-27)$$

in which T_f is the torque at the shearing stress axis (extrapolated from the linear portion of the curve), and C_f is an instrumental constant.

Example 17-8. A new ointment base was designed and subjected to rheologic analysis at 20°C in a cone-plate viscometer with an instrumental constant C of 6.277 cm^{-3} . At a cone velocity of $v = 125$ rpm the torque reading T was 1287.0 dyne cm. The torque T_f at the shearing stress axis was found to be 63.5 dyne cm.

The plastic viscosity of the ointment base at 20°C was thus calculated using equation (17-26) to be

$$U = \frac{1287 - 63.5}{125} \times 6.277 = 61.44 \text{ poise}$$

The yield value f is obtained using equation (17-27) where $C_f = 113.6 \text{ cm}^{-3}$ for the medium-size cone (radius of 2.007 cm):

$$f = 113.6 \times 63.5 = 7214 \text{ dyne/cm}^2$$

A cone and plate viscometer possesses several significant advantages over the cup and bob type of instrument. Most important is the fact that the rate of shear is constant throughout the entire sample being sheared. As a result, any chance of plug flow is avoided. The principle is illustrated in Figure 17-19, from which it may be seen that G , the rate of shear at any diameter,

is the ratio of the linear velocity Ωr to the gap width, d . Thus,

$$G = \frac{\Omega r \text{ cm/sec}}{d \text{ cm}} \quad (17-28)$$

The ratio r/d is a constant and is proportional to ψ , the angle between the cone and the plate in radians. Thus,

$$G = \frac{\Omega}{\psi} \text{ sec}^{-1} \quad (17-29)$$

and is independent of the radius of the cone. The cone angle generally ranges from 0.3° to 4° , with the smaller angles being preferred. Other advantages of a cone and plate viscometer are the time saved in cleaning and filling, and the temperature stabilization of the sample during a run. While a cup and bob viscometer may require 20 to 50 mL of a sample for a determination, the cone and plate viscometer requires a sample volume of only 0.1 to 0.2 mL. By means of a suitable attachment, it is also possible to increase and then decrease the rate of shear in a predetermined, reproducible manner. At the same time, the shear stress is plotted as a function of the rate of shear on an X-Y recorder. This is a valuable aid when determining the area of hysteresis or thixotropic coefficients, for it allows comparative studies to be run in a consistent manner. The use of this instrument in the rheologic evaluation of some pharmaceutical semisolids has been described by Hamlow,²² Gerding,²³ and Boylan.²⁴

VISCOELASTICITY

A number of methods have been used to measure the consistency of pharmaceutical and cosmetic semisolid products. The discussion in this chapter has centered on the fundamentals of continuous or steady shear rheometry of non-Newtonian materials. Oscillatory and creep measurements are also of considerable importance for investigating the properties of semisolid drug products, foods, and cosmetics that are classified as viscoelastic materials.

Continuous shear mainly employs the rotational viscometer and is plotted as flow curves (see Fig. 17-2), which provide useful information by which to characterize and control products in industry. Continuous shear does not keep the material being tested in its rheologic "ground state" but, rather, resorts to gross deformation and alteration of the material during measurement. Analysis of viscoelastic materials is designed instead not to destroy the structure, so that measurements can provide information on the intermolecular and interparticle forces in the material.

Viscoelastic measurements are based on the mechanical properties of materials that exhibit both viscous properties of liquids and elastic properties of solids. Many of the systems studied in pharmacy belong to this

class, examples being creams, lotions, ointments, suppositories, suspensions, and the colloidal dispersing, emulsifying, and suspending agents. Biologic materials such as blood, sputum, and cervical fluid also show viscoelastic properties. Whereas steady shear in rotational viscometers and similar flow instruments yield large deformations and may produce false results, oscillatory and creep methods allow the examination of rheologic materials under nearly quiescent equilibrium conditions. Davis²⁵ described creep and oscillatory methods for evaluating the viscoelastic properties of pharmaceutical materials, and Barry²⁶ reviewed these methods for pharmaceutical and cosmetic semisolids.

A semisolid is considered to demonstrate both solid and liquid characteristics. The flow of a Newtonian fluid is expressed by using equation (17-2),

$$\eta = F/G$$

relating shear stress F and shear rate G . A solid material, on the other hand, is not characterized by flow but rather by elasticity, and its behavior is expressed by the equation for a spring (derived from Hooke's law of physics):

$$E = F/\gamma \quad (17-30)$$

in which E is the elastic modulus (dyne cm^{-2}), F the stress (dyne cm^{-2}), and γ the strain, dimensionless. Using a mechanical model, a viscous fluid may be represented as movement of a piston in a cylinder (or dashpot, as it is called) filled with a liquid, as seen in Figure 17-20a. An example of a dashpot is the well-known automobile shock absorber. An elastic solid is modeled by the movement of a Hooke's spring (Fig. 17-20b). The behavior of a semisolid as a viscoelastic body may therefore be described by the combination of the dashpot and spring, as observed in Figure 17-20c. The combination of spring and shock absorber in a car, which provides a relatively smooth ride over rough roads, is analogous to the spring and dashpot of Figure 17-20c.

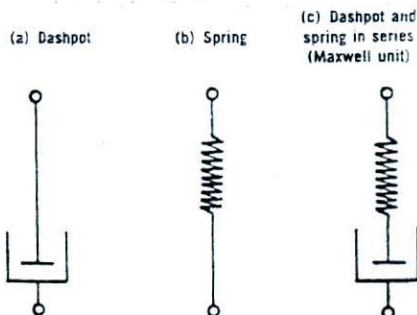


Fig. 17-20. Mechanical representation of a viscoelastic material using a dashpot and spring. The dashpot and spring in series is called a Maxwell element or unit.

This mechanical model of a viscoelastic material, a non-Newtonian material showing both viscosity of the liquid state and elasticity of the solid state, and combined in *series* is called a *Maxwell element*. The spring and dashpot may also be combined in a *parallel* arrangement as seen in Figure 17-21. This second model for viscoelasticity is known as a *Voigt element*.

As a constant stress is applied to the Maxwell unit, there is a strain on the material that can be thought of as a displacement of the spring. The applied stress may be thought of as also producing a movement of the piston in the dashpot due to viscous flow. Removal of the stress leads to complete recovery of the spring, but the viscous flow shows no recovery, that is, no tendency to return to its original state. In the Voigt model, the spring and dashpot being attached in parallel rather than series, the drag of the viscous fluid in the dashpot simultaneously influence the extension and compression of the spring which characterizes the solid nature of the material, and the strain will vary in an exponential manner with time. Strain is expressed as a deformation or *compliance*, J , of the test material in which J is strain per unit stress. The compliance of a viscoelastic material following the Voigt model is given as a function of time t by the expression

$$J = J_{\infty}(1 - e^{-t/\tau}) \quad (17-31)$$

in which J_{∞} is the compliance or strain per unit stress at infinite time and τ is viscosity per unit modulus, η/E (dyne sec $\text{cm}^{-2}/\text{dyne cm}^{-2}$), which is called *retardation time* and has the unit of sec.

The mechanical models, Maxwell and Voigt, representing viscoelastic behavior in two different ways, may be combined into a generalized model to incorporate all possibilities of flow and deformation of non-Newtonian materials. One of several Voigt units may be combined with Maxwell elements to represent the changes that a pharmaceutical solid, such as an ointment or cream, undergoes as it is stressed. As observed in Figure 17-22, two Voigt elements are combined with a Maxwell element to reproduce the behavior of a sample of wool fat²⁵ at 30° C. The compliance J as a

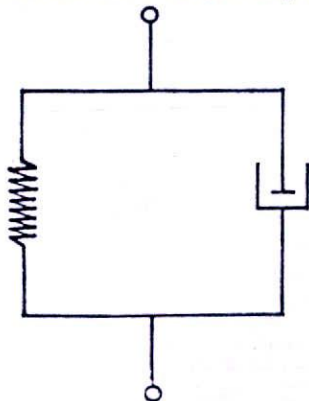


Fig. 17-21. Spring and dashpot combined in parallel as a mechanical model of a viscoelastic material, known as a *Voigt element*.

function of time is measured with an instrument known as a *creep viscometer* (Fig. 17-23) and is plotted in Figure 17-22 to obtain a *creep curve*. The creep curve is observed to be constructed of three parts, first a sharply rising portion AB corresponding to the elastic movement of the uppermost spring; second, a curved portion BC , a viscoelastic region representing the action of the two Voigt units; and third, a linear portion CD corresponding to movement of the piston in the dashpot at the bottom of the Maxwell-Voigt model representing viscous flow.

The compliance equation corresponding to the observed behavior of wool fat (Fig. 17-22), as simulated by the Maxwell-Voigt model (insert (a) in Fig. 17-22), is

$$J = \frac{\gamma_0}{F} + J_m(1 - e^{-t/\tau_m}) + J_n(1 - e^{-t/\tau_n}) + \frac{\gamma}{F} \quad (17-32)$$

in which γ_0 is the instantaneous strain and F the constant applied shear stress.^{25,26} The quantity, γ_0/F , is readily obtained from the experimental curve (region AB) in Figure 17-22. The viscoelastic region of the curve (BC) is represented by the intermediate term of equation (17-32), in which J_m and J_n are the mean compliance of bonds in the material and τ_m and τ_n are the mean retardation times for the two Voigt units of Figure 17-22. It is sometimes found that three or more Voigt units are needed in the model to reflect the observed behavior of the material. The final term of equation (17-32) corresponds to the linear portion, CD , of the creep curve. This section represents a condition of Newtonian compliance in which the rupture of bonds leads to the flow of the material, where F is the constant applied stress and γ is the shear strain in this region of the curve.

When stress is removed by the operator of the creep rheometer (Fig. 17-23), a recovery DEF of the sample is obtained. It is composed of an instantaneous elastic recovery, DE , equivalent to AB , followed by an elastic recovery region EF equivalent to BC . In the creep compliance curve of Figure 17-22, flow occurs in region CD , irreversibly destroying the structure, and in the recovery curve this portion is not reproduced. By such an analysis, Davis²⁵ obtained the elastic moduli (insert (a) of Figure 17-22) $E_0 = 2.7 \times 10^4$ dyne cm^{-1} , $E_1 = 5.4 \times 10^4$ dyne cm^{-1} , and $E_2 = 1.4 \times 10^4$ dyne cm^{-1} ; and the three viscosities, $\eta_1 = 7.2 \times 10^5$ poise, $\eta_2 = 4.5 \times 10^6$ poise, and $\eta_0 = 3.1 \times 10^7$ poise for wool fat.

The creep curve used to measure the viscoelasticity of non-Newtonian pharmaceutical, dermatologic, and cosmetic materials may shed some light on the molecular structure of the materials and therefore provide information for modification and improvement of these vehicles. Creep compliance curves were used by Barry²⁶ to study the changes with temperature in

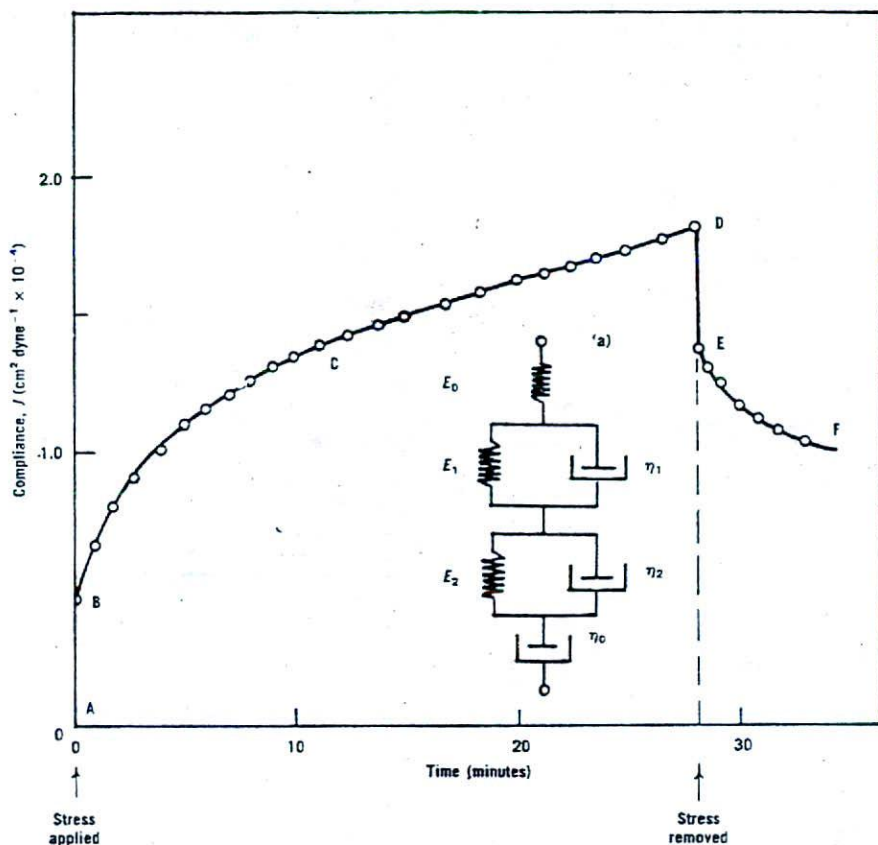


Fig. 17-22. A creep curve obtained by analyzing a sample of wool fat in a creep viscometer (Fig. 17-23) at 30° C. The creep curve results from a plot of compliance, J , equation (17-31), against the time in minutes during which a stress is applied to the sample. (a) The insert shows the combination of Maxwell and Voigt elements required to represent the viscoelasticity of the wool fat sample. E_0 , E_1 , and E_2 , the spring moduli, may be calculated from the plot and by use of equation (17-32) and the three viscosities η_1 , η_2 , and η_0 . (From S. S. Davis, *Pharm. Acta Helv.* 49, 161, 1974, reproduced with permission of the copyright owner.)

samples of white petrolatum (White Soft Paraffin, British Pharmacopoeia) as observed in Figure 17-24. The behavior was complex, requiring five Voigt units and one Maxwell element to describe the observed creep compliance curves at 5° and 25° C, and three Voigt units at 45° C where some of the structure had been destroyed by melting. Three curves are characteristic of the crystalline bonding and the interaction of crystalline and amorphous material that constitute petrolatum. The curves were automatically plotted on an X-Y recorder as the material was stressed in the creep viscometer. The open circles plotted along the lines of Figure 17-24 were obtained by use of an equation similar to equation (17-32), showing the accuracy with which the creep curves can be reproduced by a theoretic model of Voigt and Maxwell units.

Another dynamic rheologic method that does not disturb the structure of a material is that of oscillatory

testing.²⁵⁻²⁸ A thin layer of material is subjected to an oscillatory driving force in an apparatus such as that shown in Figure 17-25. Another instrument of oscillatory analysis is the rheogoniometer (Martin Sweets Co., Louisville, Ky.). The shearing stress produced by the oscillating force in the membrane apparatus of Figure 17-25 results in a shear rate proportional to the surface velocity of the material. The viscoelastic behavior of materials obtained by oscillatory shear measurements may be analyzed by an extension of the Maxwell spring and dashpot model.

Steady shear methods involving rotational viscometers tend to break down materials under analysis, and although they yield useful data on thixotropy and yield stress, for example, they do not provide information about the original structure and bonding in pharmaceutical and cosmetic semisolids. Viscoelastic analysis performed by creep or oscillatory methods is particu-

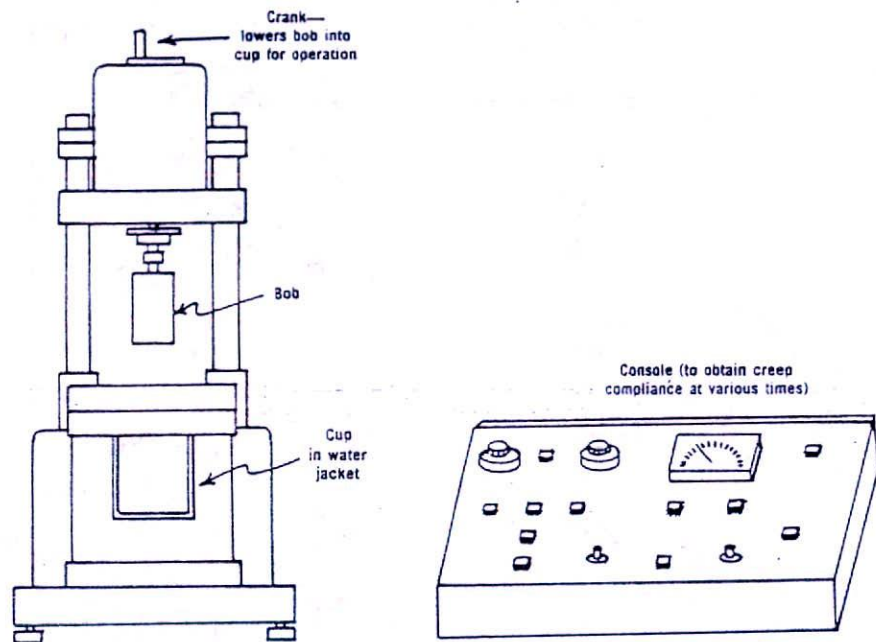


Fig. 17-23. Main components of a creep viscometer used to obtain creep compliance curves such as those found in Figures 17-22 and 17-24.

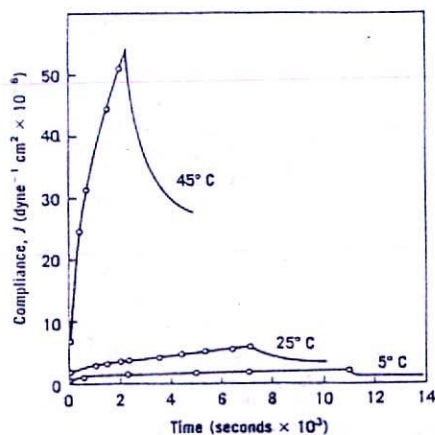


Fig. 17-24. Creep compliance curves of soft white paraffin (British Pharmacopoeia) at three temperatures. (From B. W. Barry, in *Advances in Pharmaceutical Sciences*, H. S. Bean, A. H. Beckett and J. E. Carless, Eds., Vol. 4, Academic Press, New York, 1974, p. 36, reproduced with permission of the copyright owner.)

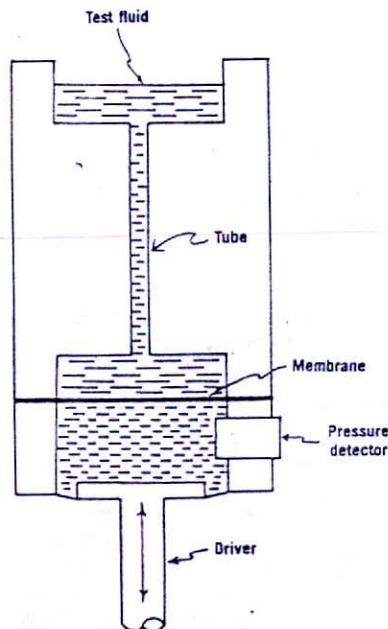


Fig. 17-25. Apparatus for oscillatory testing of viscoelastic materials. (From G. B. Thurston and A. Martin, *J. Pharm. Sci.* 67, 1499, 1978, reproduced with permission of the copyright owner.)

larly useful for studying the structure of liquid and semisolid emulsions and gels.²⁷ Viscoelastic measurements can also be used to measure the rheologic changes occurring in a cream after it is broken down in various stages by milling, incorporation of drugs, or by spreading on the skin.

Radebaugh and Simonelli²⁹ studied the viscoelastic properties of anhydrous lanolin, which were found to be a function of strain, shear frequency, shear history, and temperature. The energy of activation E_a was calculated for the structural changes of the lanolin sample, which was found to undergo a major mechanical transition between 10° and 15° C. The E_a for the transition was ≈ 90 kcal, that expected for glass transition. But rather than a sharp change from a rubbery to a glasslike state, anhydrous lanolin appeared to change to a state less ordered than glass. Glass-rubber transition and the glass transition temperature are discussed on pages 586 to 588. The viscoelastic properties were determined using a Rheometrics mechanical spectrometer (RMS 7200, Rheometrics, Inc., Union, N.J.). The rheometer introduces a definite deformation into the sample at a specified rate and at a chosen temperature.

Viscoelastic methods are also of value in the analysis of sputum, for the design of mucolytic agents in the treatment of bronchitis, asthma, and cystic fibrosis. Other biologic fluids such as blood, vaginal material, and synovial fluids may be analyzed by viscoelastic test methods. The unsteady shear to which synovial fluids are subjected in the body during the movement of leg and arm joints requires the elastic properties of these fluids, in addition to viscous properties that are observed only in steady shear. Thurston and Greiling³⁰ used oscillatory shear to analyze cases of noninflammatory and inflammatory joint disease associated with arthritis. The macromolecule hyaluronic acid is primarily responsible for the high viscosity and non-Newtonian character of synovial fluid and gives it simple Newtonian rather than the desired non-Newtonian properties. Changes in viscoelasticity of synovial fluids, measured in the oscillatory instrument shown in Figure 17-25, may therefore serve as sensitive indicators of joint disease.

PSYCHORHEOLOGY

In addition to desirable pharmaceutical and pharmacologic properties, topical preparations must meet criteria of feel, spreadability, color, odor, and other psychologic and sensory characteristics. Workers in the food industry have long tested products such as butter, chocolate, mayonnaise, and bread dough for proper consistency during manufacture, packaging, and end use. Sensations in the mouth, between the fingers, and on the skin are important considerations for manufacturers of foods, cosmetics, and dermatologic products.

Scott-Blair³¹ discussed *psychorheology* (as this sub-

ject is called) in the food industry. Kostenbauder and Martin³² assessed the spreadability of ointments in relation to their rheologic properties. In consultation with dermatologists, they divided the products into three classes. Class I products were soft, mainly for ophthalmic use; Class II included common medicated ointments of intermediate consistency; and Class III involved stiff protective products for use in moist ulcerative conditions. The yield values and plastic viscosity for each class of product were reported.

Boylan³⁴ has shown that the thixotropy, consistency, and yield value of bacitracin ointment, USP, decreased markedly as the temperature was raised from 20° to 35° C. Thus, while a product may be sufficiently thixotropic in its container, this property can be lost following application to the skin.

Barry et al.³³ carried out sensory testing on topical preparations. They used a panel to differentiate textural parameters and established rheologic methods for use in industry as control procedures to maintain uniform skin feel and spreadability of dermatologic products. Cussler et al.³⁴ studied the texture of non-Newtonian liquids of widely different rheologic properties applied to the skin. It was found that the consistency of a material could be accurately assessed by a panel of untrained subjects by the use of only three attributes: smoothness, thinness, and warmth. Smoothness was related to a coefficient of friction, and thinness to non-Newtonian viscous parameters that could be measured with appropriate instruments. The characteristic of warmth was found to be sufficiently complex to require further study.

APPLICATIONS TO PHARMACY

The rheologic behavior of poloxamer vehicles was studied as a function of concentration over a temperature range of 5° to 35° C using a cone-plate viscometer.³⁵ Poloxamers are block polymers of BASF Wyandotte Corp., having the chemical structure



Poloxamers with a wide range of molecular weights are available as Pluronic[®]. Some of the poloxamers are used in the dermatologic bases or topical ophthalmic preparations because of their low toxicity and their ability to form clear water-based gels.

The aqueous solubility of the poloxamers decreases with an increase in temperature, the hydration of the polymer being reduced by breaking of hydrogen bonds at higher temperatures. The desolvation that results, together with the entanglement of the polymer chains, probability accounts for the gel formation of the poloxamers.

A linear relationship was found between shear rate and shear stress (Newtonian behavior) for the poloxamer vehicles in the sol state, which exists at low

concentrations and low temperatures. As the concentration and temperature were increased, some of the poloxamers exhibited a sol-gel transformation and became non-Newtonian in their rheologic character. The addition of sodium chloride, glycerin, or propylene glycol resulted in increased apparent viscosities of the vehicles.

Polymer solutions may be used in ophthalmic preparations, as wetting solutions for contact lens, and as tear replacement solutions for the condition known as *dry eye syndrome*. Both natural (e.g., dextran) and synthetic (e.g., polyvinyl alcohol) polymers are used with the addition of various preservatives. A high-molecular-weight preparation of sodium hyaluronate at concentrations of 0.1 to 0.2% has been introduced to overcome the dry eye condition.

For high-polymer solutions, the viscosity levels off to a *zero shear viscosity* (a high viscosity) at low shear rates. The viscosity decreases as the shear rate is increased, for the normally twisted and matted polymer molecules align in the streamlined flow pattern and exhibit pseudoplasticity or shear thinning.

Bothner and colleagues³⁶ suggest that a suitable tear substitute should have shear thinning properties as do natural tears, to conform to the low shear rate during non-blinking and the very high shear rate during blinking. The low viscosity at high shear rates produces lubrication during blinking, and the high viscosity at zero shear rate prevents the fluid from flowing away from the cornea when the lids are not blinking. Using a computer-controlled Couette viscometer, the rheologic properties of eight commercial tear substitutes, together with 0.1% and 0.2% solutions of sodium hyaluronate, were studied. For five of the commercial products, the viscosity was independent of shear rate; thus, these products behaved as Newtonian liquids. Two products showed slight shear thinning at high shear rates. Only the commercial product Neo-Tears and the two noncommercial sodium hyaluronate solutions showed the desired pseudoplastic behavior. For Neo-Tears the viscosity at high shear rate, 1000 sec^{-1} , was threefold that at zero shear. For 0.1% sodium hyaluronate the value was fivefold and for 0.2% sodium hyaluronate it was thirtyfold. Therefore, sodium hyaluronate appears to be an excellent candidate as a tear replacement solution.

The rheologic properties of suppositories at rectal temperatures can influence the release and bioabsorption of drugs from suppositories, particularly those having a fatty base. Grant and Liversidge³⁷ studied the characteristics of triglyceride suppository bases at various temperatures using a rotational rheometer. Depending on the molten (melted) character of the base, it behaved either as Newtonian material or as a plastic with thixotropy.

Fong-Spaven and Hollenbeck³⁸ studied the rheologic properties as a function of the temperature of mineral

oil-water emulsions stabilized with triethanolamine stearate (TEAS). The stress required to maintain a constant rate of shear was monitored as the temperature was raised from 25° to 75° C. Unexpected, but reproducible, discontinuities in the plots of temperature versus apparent viscosity were obtained using a Brookfield digital viscometer (see p. 465), and were attributed possibly to shifts in the liquid crystalline (pp. 36–37) structures. As seen in Figure 17–26, where apparent viscosity is plotted versus temperature for a 5% TEAS mineral oil-water emulsion, the viscosity decreases as temperature is raised to about 48° C. The viscosity reverses and increases to a small peak at 54° C, and then decreases again with increasing temperature. This unusual behavior is considered to result from gel formation, which stabilizes the internal phase. Liquid crystalline structures of TEAS exist and at higher temperatures the structures disintegrate or "melt" to form a large number of TEAS molecules in a gel-like arrangement that exhibits an increased resistance to flow. As the temperature rises above 54° C the gel structure is gradually destroyed and the viscosity again decreases, as shown in Figure 17–26.

Patterned after the manufacture and use of cosmetic sticks, solidified sodium stearate-based sticks were prepared and tested for topical application using a Ferranti-Shirley cone-plate viscometer. The sticks contained propylene glycol (PG), polyethylene glycol 400 and polyethylene glycol 600 (PEG 400 and PEG 600) as humectants, and the topically active drugs panthenol, chlorphenesin, and lignocaine. Thixotropic breakdown was much lower in these medicated sticks than in comparable bases. The addition of the three topical drugs to the stearate-based sticks caused changes in the yield values, thixotropy, and plastic viscosity; possible reasons for the changes were advanced.³⁹

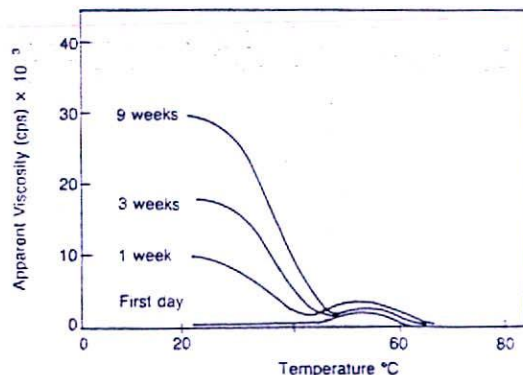


Fig. 17–26. Viscosity versus temperature plots of an oil-water emulsion over a period of 9 weeks. (From F. Fong-Spaven and R. G. Hollenbeck, *Drug Dev. Ind. Pharm.* 12, 289, 1986, reproduced with permission of the copyright owner.)

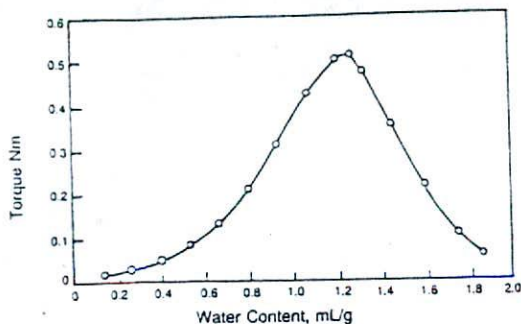


Fig. 17-27. Changes of torque in a mixer torque rheometer as water is added to a mixture of powders. (From R. C. Rowe and G. R. Sadeghnejad, *Int. J. Pharm.* 38, 227, 1987, reproduced with permission of the copyright owner.)

Rowe and Sadeghnejad⁴⁰ studied the rheologic properties of microcrystalline cellulose,* an ingredient incorporated in wet powder masses to facilitate the granulation process in the manufacture of tablets and granules. The authors designed a *mixer torque rheometer* to measure the torque changes as water was added to the powder mixture. (*Torque* is the force acting to produce rotation of a body.) As the mixture became wetter the torque increased until the mass was saturated, then decreased with further addition of water as a slurry (suspension) was formed. A plot of torque in Newton meters (1 Nm = 1 joule) against increasing water content produced a bell-shaped curve, as shown in Figure 17-27. This behavior was explained, according to the authors, by the three states of liquid saturation of a powder mass, as described by Newitt and Conway-Jones.⁴¹

With the early addition of liquid, a *pendular state* exists (see Fig. 17-28) with lenses of liquid at the contact points of the particles. The liquid forces out some of the air originally filling all the spaces between the particles. As more liquid is added, a mixture of liquid and air exists between the particles to produce the *funicular state*. The torque on the mixer increases for these two conditions until the end of the funicular state. The pores are then filled with liquid to yield the *capillary state*, and with the addition of more liquid the torque decreases as a slurry (suspension) is produced (*liquid-droplet state*). These stages of saturation are depicted schematically in Figure 17-28.

The three microcrystalline celluloses from different sources⁴⁰ exhibited essentially the same plot of torque versus water added (see Fig. 17-27). Yet the curves, only one of three shown here, rose to slightly different heights and the maxima occurred at different amounts of water added.

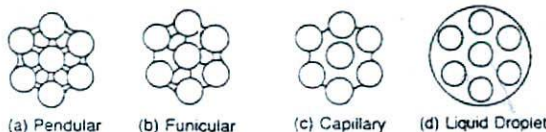


Fig. 17-28. The states of liquid saturation of a powder. (a) *Pendular* state with lenses of liquid at the contact points of the particles. (b) A mixture of liquid and air between the particles, producing the *funicular* state. (c) Pores filled with liquid to yield the *capillary* state. (d) Liquid droplets completely enveloping particles (the *liquid-droplet* state). (Modified from D. M. Newitt and J. M. Conway-Jones, *Trans. Inst. Chem. Eng.* 36, 422, 1958.)

An account of the rheology of suspensions, emulsions, and semisolids is presented in Chapter 18, while the flow properties of powders have been dealt with in Chapter 16. Consideration has also been given in Chapter 15 to the rheology of colloid materials, which find wide application in pharmacy as suspending agents. Some of the rheologic aspects of parenteral suspensions and emulsions have been considered by Boylan.²⁴

A summary of the major areas of product design and processing in which rheology is significant are listed in Table 17-3. While the effects of processing can affect the flow properties of pharmaceutical systems, a detailed discussion of this area is outside the scope of our text. For an account of this topic, as well as a comprehensive presentation of the theoretic and instrumental aspects of rheology, refer to the review by Martin et al.³ The theory and application of viscoelasticity have been briefly reviewed in the previous section. Detailed discussions of this approach are given in the references cited.

TABLE 17-3. *Pharmaceutical Areas in which Rheology is Significant**

1. Fluids
 - a. Mixing
 - b. Particle-size reduction of disperse systems with shear
 - c. Passage through orifices, including pouring, packaging in bottles, and passage through hypodermic needles
 - d. Fluid transfer, including pumping and flow through pipes
 - e. Physical stability of disperse systems
2. Quasisolids
 - a. Spreading and adherence on the skin
 - b. Removal from jars or extrusion from tubes
 - c. Capacity of solids to mix with miscible liquids
 - d. Release of the drug from the base
3. Solids
 - a. Flow of powders from hoppers and into die cavities in tableting or into capsules during encapsulation
 - b. Packagability of powdered or granular solids
4. Processing
 - a. Production capacity of the equipment
 - b. Processing efficiency

*With permission from A. Martin, G. S. Banker and A. H. C. Chun, in *Advances in Pharmaceutical Sciences*, H. S. Bean, A. H. Beckett and J. E. Carless, Eds., Academic Press, London, 1964, Chapter 1. Copyright, Academic Press Inc. (London) Ltd.

*Avicel of FMC Corp., Philadelphia; Emcocel of Finnish Sugar Co., Helsinki; Unimac of Unitika Rayon, Osaka.

reading T was found to be 120 at an rpm of 55. The instrument constant C is 1.168 for the large cone used. Compute the viscosity.

(b) An o/w mineral oil emulsion was found to show plastic flow when analyzed in the cone-plate viscometer. Calculate the plastic viscosity of the emulsion using the following data: torque, $T = 110$ at rpm = 200 and $T_f = 25$ at rpm = 0, $C = 1.168$.

(c) Calculate the yield value f for the emulsion in part (b). The yield value is obtained by the use of the equation $f = 0.122 \times T_f$ when the large cone is employed in the Ferranti-Shirley viscometer.

Answers: (a) 2.55 poise; (b) 0.50 poise; (c) 3.1 dyne/cm²

17-11. To obtain the Newtonian viscosity of three oils in a cone-plate viscometer, the following cone speeds, v (rpm) were held constant and the torque values, T (dyne cm), for the oils were obtained at 25° C.

Data for Problem 17-11

Oil number	1	2	3
Torque, T (dyne cm)	169	95.0	49.4
Cone speed, v (rpm)	73.0	73.0	73.0

The large cone was used, having an instrumental constant $C = 1.168$. The constant, C , takes account of the dimensions such that when T is given in dyne cm and v in rpm, the viscosity is given in poise.

Partial Answer: For oil no. 1, $\eta = 2.704$ poise

17-12. The yield value f and plastic viscosity U of a gel of lithium stearate and liquid petrolatum were determined in a cone-plate viscometer at 23° C following equations (17-26) and (17-27) on page 466. T_f , the torque reading at the yield value, i.e., the torque extrapolated to the shearing stress axis, was found experimentally to have a value of 34.51 dyne cm.

The instrumental constant C_f is obtained from the equation

$$C_f = \frac{3S}{2\pi R^3}$$

in which S is a torque spring constant, a dimensionless number equal to 1923; R is the radius of the cone, 2.007 cm; and $\pi = 3.14159$, the ratio of the circumference to the diameter of a circle.

(a) What is the value of the instrumental constant, C_f ?

(b) Calculate the yield value f for the gel for which T_f is 34.51 dyne cm.

(c) If T , the torque reading, is found to be 137.74 dyne cm at a rotational velocity of the cone of 73.0 rpm and $C = 6.277$ cm⁻³, what is the plastic viscosity of the gel?

Answers: (a) $C_f = 113.57$ cm⁻³; (b) $f = 3919$ dyne cm⁻²; (c) $U = 8.876$ poise

17-13. Use an Ostwald viscometer at 20° C the time for the flow of water through the apparatus is 297.3 seconds. When the instrument

was dried and filled with carbon disulfide, the time of flow was 85.1 sec. The density of water at 20° C is 0.9982 and that of CS₂ is 1.2632 g/mL. The viscosity of water at 20° C is 1.002 cp. What is the viscosity of carbon disulfide at 20° C.

Answer: Check your result for the viscosity of CS₂ at 20° C against the value in a handbook of chemistry.

17-14. (a) The time for water to flow through an Ostwald pipette at 20° C was 297.3 sec. The density of water at 20° C is 0.9982 and the density of a sample of olive oil is 0.910 g/mL. The viscosity of water at 20° C is 1.002 cp and the viscosity of the sample of olive oil is 84.0 cp. How long will it take for the olive oil to flow through the Ostwald pipette at 20° C?

(b) Would you reason that water was a good choice to use as the reference liquid in this experiment? What other liquid might you choose and on what basis would you choose it? Would it be wise to use an Ostwald pipette with a larger or smaller bore to determine the viscosity of olive oil?

Answer: 27339 sec or 7.59 hours

17-15. The radius of a vascular capillary in the body is approximately 1 to $10 \mu\text{m}$ (10^{-4} to 10^{-3} cm), the viscosity of blood at 37° C is about 0.04 dyne sec cm⁻², and the average rate of blood flow V/t is 1.20×10^{-6} cm³ sec⁻¹. See Figure 17-12 for a schematic of the anatomy of the heart, capillaries, and other vessels. What is the pressure drop in mm Hg over a distance of 0.5 cm along the capillary with a radius of 8.45×10^{-4} cm? Use the Poiseuille law (equation (17-13)).

Answer: $\Delta P = 90$ mm Hg. Now, convert to SI units: $\Delta P = 1.20 \times 10^4$ N m⁻²

17-16. The viscosity η of whole blood at body temperature, 37° C (310° K), is 0.04 poise (dyne sec/cm²). The pressure drop ΔP is 20 mm Hg, or 2.67×10^4 dyne/cm², over a distance ℓ of 3.2 mm in the capillary. The radius, r , of the capillary is 0.0012 cm. (Note: From a table of conversion factors 20 mm Hg \times 1333.25 dyne/cm²/mm Hg = 2.67×10^4 dyne/cm².) What is the volume rate, V/t , of blood flow in the capillary? The flow of blood in the body is shown in Figure 17-12.

Answer: $V/t = 1.70 \times 10^{-6}$ cm³/sec

17-17. The volume rate of blood flow in the aorta (see Figure 17-12) of a patient where the radius of the artery is approximately 0.5 cm was measured and found to be $V/t = 4.8$ cm³/sec. The pressure difference ΔP over a distance of $\ell = 1$ cm was 0.0052 mm Hg (Note: 0.0052 torr (or mm Hg) \times 1333.22 (dyne/cm²)/mm Hg = 6.93 dyne/cm².) Calculate the viscosity of the patient's blood at 37° C using the Poiseuille equation, page 462.

Answer: The viscosity of the patient's blood was also measured in a capillary viscometer at 37° C and found to be 0.0372 poise. How does your calculated result compare with this experimentally determined viscosity of the blood?

17-18. Explain how one would set up a sensory testing panel and carry out a psychoneurologic study to correlate the properties of commercial hand lotions in relation to client acceptance.

Answer: See several of the works listed under references 31 to 34.

rather large number. The student should not be surprised to find η' in the thousands or millions of poise.

Another approach to solving for F' is as follows. One begins with the expression $\ln G = -\ln \eta' - N \ln F'$ and from regression analysis using this equation one obtains $\eta' = 106,724$ and $N = 2.6239$. Therefore, using $F'^N = \eta' G$, for $G = 1875 \text{ sec}^{-1}$,

$$F'^{2.6239} = (106,724)(1875) = 2.00107 \times 10^8$$

Using the y^x key on a hand calculator, the student may run through the exercise, $2^3 = 8$; therefore, $2 = 8^{1/3}$. With this kind of operation applied in our problem, $F'^{2.6239} = 200,107,000$, $F' = 200,107,000^{1/2.6239} = 200,107,000^{0.381112}$, $F' = 1458 \text{ dyne/cm}^2$.

17-4. The following data were obtained at 25° C for a plastic system by means of a cup-and-bob viscometer. Calculate the yield value, f , and the plastic viscosity U of this material.

Data for Problem 17-4

G , rate of shear (sec ⁻¹)	F , shearing stress (dynes cm ⁻²)
100	10,200
200	11,200
300	12,200
400	13,200
500	14,200
600	15,200

Answer: f (yield value) = 9200 dyne cm⁻²; $U = 10$ poise

17-5. Based on Figure 17-5, calculate the plastic viscosities U_1 and U_2 and the thixotropic coefficient B , given the following data obtained at 25° C:

The constant rate of shear G is 240 sec⁻¹, while t_1 and t_2 are 50 and 30 seconds, respectively. Points c and d in Figure 17-5 have shearing stresses F of 9440 and 6728 dyne cm⁻², respectively. The yield value f in both cases is 5000 dyne cm⁻², since both down-curves intersect the F -axis at this shearing stress.

Answer: $U_1 = 18.5$ poise; $U_2 = 7.2$ poise; $B = 24$ dyne sec/cm²

17-6. A sample of petrolatum was analyzed in a Stormer viscometer at 25° C. To obtain the coefficient of thixotropic breakdown M , two upcurves were run, the upper curve having a top rate of shear of $v_1 = 543$ rpm and the lower of $v_2 = 325$ rpm. The values of the constants were $K_u = 40.5$ and $K_f = 15.9$. The driving weights in grams w_1 and w_2 for the two shear rates v_1 and v_2 were found from the flow curves to be $w_1 = 269$ g and $w_2 = 225$ g. The yield value intercepts for the two curves were $w_{f1} = 124$ g and $w_{f2} = 96$ g. Compute the plastic viscosities, yield values, and the coefficient of thixotropic breakdown, M .

Answer: $U_1 = 11$ poise, $U_2 = 16$ poise; $f_1 = 1972$ dyne cm⁻², $f_2 = 1526$ dyne cm⁻²; $M = 10$ dyne sec cm⁻²

17-7. In calibrating the cup-and-bob combination of a Stormer viscometer, an N.B.S. Newtonian oil with a viscosity of 200.0 poise at 20° C was used. With a weight of 1600 g on the weight hanger, the bob rotated at 400 rpm. Compute the instrumental constant K_v .

Answer: 50 poise/(g min)

17-8. To calibrate rotational viscometers, viscosity data are collected⁴ using a standardized Newtonian oil from the National Bureau of Standards or from other reference sources. The carefully determined viscosity of oil #4 at 25° C is 1.455 poise. The weights in grams placed on the weight hanger of a Stormer viscometer and the velocity (v) of the rotating cylinder in revolutions per minute (rpm) are recorded here at 25° C.

Data (a) for Problem 17-8

Mass (g)	50	100	150	200	250	300
rpm (v)	67.5	137	202	270	337	400

Plot the velocity in rpm (vertical or y -axis of the graph) versus mass in grams on the weight hanger of the Stormer viscometer (horizontal or x -axis). The equation for calculating Newtonian viscosity is

$$\eta = K_v \left(\frac{\text{mass in grams}}{\text{velocity in rpm}} \right) \quad (17-33)$$

or

$$\text{rpm} = \frac{K_v}{\eta} (\text{mass}) \quad (17-34)$$

The slope (y/x) of the line, using linear regression, provides the value of rpm/mass = K_v/η , and knowing the viscosity at 25° C of the oil viscosity standard, it is possible to obtain an accurate value of the instrumental constant, K_v , using the experimentally obtained data in the table above.

Once the constant K_v is found for the Stormer viscometer, it is possible to calculate the viscosity of a Newtonian oil of unknown consistency. The slopes (rpm/mass) of the plots of rpm versus mass for these N.B.S. oils at 25° C are:

Data (b) for Problem 17-8

Oil number	1	6	9
Slope (K_v/η)	0.2180	2.7933	18.5185

The Newtonian viscosities of these oils at 25° C have been determined by the National Bureau of Standards and have the values

Data (c) for Problem 17-8

Oil number	1	6	9
Viscosity (poise)	9.344	0.6725	0.09134

Using the K_v value calculated for the Stormer viscometer, compute the viscosities of the three Newtonian oils using equation (17-33). Compare these results with the accurate viscosity values obtained by the National Bureau of Standards.

Partial Answer: $K_v = 1.9376$; viscosity of oil no. 1 = 8.970 poise. From the table above, the N.B.S. value for oil number 1 is 9.344 poise. Our result is therefore in error by 4%.

17-9. A liquid flavoring concentrate for a cough syrup was analyzed at 25° C in a Stormer viscometer having an instrumental constant, $K_v = 8.460$ poise/(g min). The rates of shear in rpm for various weights on the weight hanger are:

Data for Problem 17-9

Weights (g)	160	240	320	480
rpm (v)	227	340	452	680

Plot the rpm versus weight on the weight hanger and calculate the viscosity of the flavoring agent. Is it a Newtonian or non-Newtonian liquid? The slope, (rpm/wt), may be obtained by linear regression or by the two-point formula (p. 8, 9).

Answer: $\eta = 597.7$ cps. A plot of the data shows the liquid to be Newtonian.

17-10. (a) The Ferranti-Shirley cone-plate viscometer was used to determine the viscosity of a Newtonian oil at 30° C. The torque

reading T was found to be 120 at an rpm of 55. The instrument constant C is 1.168 for the large cone used. Compute the viscosity.

(b) An o/w mineral oil emulsion was found to show plastic flow when analyzed in the cone-plate viscometer. Calculate the plastic viscosity of the emulsion using the following data: torque, $T = 110$ at rpm = 200 and $T_p = 25$ at rpm = 0, $C = 1.168$.

(c) Calculate the yield value f for the emulsion in part (b). The yield value is obtained by the use of the equation $f = 0.122 \times T_p$ when the large cone is employed in the Ferranti-Shirley viscometer.

Answers: (a) 2.55 poise; (b) 0.50 poise; (c) 3.1 dyne/cm²

17-11. To obtain the Newtonian viscosity of three oils in a cone-plate viscometer, the following cone speeds, v (rpm) were held constant and the torque values, T (dyne cm), for the oils were obtained at 25° C.

Data for Problem 17-11

Oil number	1	2	3
Torque, T (dyne cm)	169	95.0	49.4
Cone speed, v (rpm)	73.0	73.0	73.0

The large cone was used, having an instrumental constant $C = 1.168$. The constant, C , takes account of the dimensions such that when T is given in dyne cm and v in rpm, the viscosity is given in poise.

Partial Answer: For oil no. 1, $\eta = 2.704$ poise

17-12. The yield value f and plastic viscosity U of a gel of lithium stearate and liquid petrolatum were determined in a cone-plate viscometer at 23° C following equations (17-26) and (17-27) on page 466. T_p , the torque reading at the yield value, i.e., the torque extrapolated to the shearing stress axis, was found experimentally to have a value of 34.51 dyne cm.

The instrumental constant C_f is obtained from the equation

$$C_f = \frac{3S}{2\pi R^3}$$

in which S is a torque spring constant, a dimensionless number equal to 1922; R is the radius of the cone, 2.007 cm; and $\pi = 3.14159$, the ratio of the circumference to the diameter of a circle.

(a) What is the value of the instrumental constant, C_f ?

(b) Calculate the yield value f for the gel for which T_p is 34.51 dyne cm.

(c) If T , the torque reading, is found to be 137.74 dyne cm at a rotational velocity of the cone of 73.0 rpm and $C = 6.277$ cm⁻³, what is the plastic viscosity of the gel?

Answers: (a) $C_f = 113.57$ cm⁻³; (b) $f = 3919$ dyne cm⁻²; (c) $U = 8.876$ poise

17-13. Use an Ostwald viscometer at 20° C the time for the flow of water through the apparatus is 297.3 seconds. When the instrument

was dried and filled with carbon disulfide, the time of flow was 85.1 sec. The density of water at 20° C is 0.9982 and that of CS₂ is 1.2632 g/mL. The viscosity of water at 20° C is 1.002 cp. What is the viscosity of carbon disulfide at 20° C.

Answer: Check your result for the viscosity of CS₂ at 20° C against the value in a handbook of chemistry.

17-14. (a) The time for water to flow through an Ostwald pipette at 20° C was 297.3 sec. The density of water at 20° C is 0.9982 and the density of a sample of olive oil is 0.910 g/mL. The viscosity of water at 20° C is 1.002 cp and the viscosity of the sample of olive oil is 84.0 cp. How long will it take for the olive oil to flow through the Ostwald pipette at 20° C?

(b) Would you reason that water was a good choice to use as the reference liquid in this experiment? What other liquid might you choose and on what basis would you choose it? Would it be wise to use an Ostwald pipette with a larger or smaller bore to determine the viscosity of olive oil?

Answer: 27339 sec or 7.59 hours

17-15. The radius of a vascular capillary in the body is approximately 1 to 10 μ m (10^{-4} to 10^{-3} cm), the viscosity of blood at 37° C is about 0.04 dyne sec cm⁻², and the average rate of blood flow V/t is 1.20×10^{-6} cm³ sec⁻¹. See Figure 17-12 for a schematic of the anatomy of the heart, capillaries, and other vessels. What is the pressure drop in mm Hg over a distance of 0.5 cm along the capillary with a radius of 8.45×10^{-4} cm? Use the Poiseuille law (equation (17-13)).

Answer: $\Delta P = 90$ mm Hg. Now, convert to SI units: $\Delta P = 1.20 \times 10^4$ N m⁻²

17-16. The viscosity η of whole blood at body temperature, 37° C (310° K), is 0.04 poise (dyne sec/cm²). The pressure drop ΔP is 20 mm Hg, or 2.67×10^4 dyne/cm², over a distance l of 3.2 mm in the capillary. The radius, r , of the capillary is 0.0012 cm. (Note: From a table of conversion factors 20 mm Hg \times 1333.25 dyne cm⁻²/mm Hg = 2.67×10^4 dyne cm⁻².) What is the volume rate, V/t , of blood flow in the capillary? The flow of blood in the body is shown in Figure 17-12.

Answer: $V/t = 1.70 \times 10^{-6}$ cm³/sec

17-17. The volume rate of blood flow in the aorta (see Figure 17-12) of a patient where the radius of the artery is approximately 0.5 cm was measured and found to be $V/t = 4.8$ cm³/sec. The pressure difference ΔP over a distance of $l = 1$ cm was 0.0052 mm Hg (Note: 0.0052 torr (or mm Hg) \times 1333.22 (dyne/cm²)/mm Hg = 6.93 dyne/cm².) Calculate the viscosity of the patient's blood at 37° C using the Poiseuille equation, page 462.

Answer: The viscosity of the patient's blood was also measured in a capillary viscometer at 37° C and found to be 0.0372 poise. How does your calculated result compare with this experimentally determined viscosity of the blood?

17-18. Explain how one would set up a sensory testing panel and carry out a psychorheologic study to correlate the properties of commercial hand lotions in relation to client acceptance.

Answer: See several of the works listed under references 31 to 34.